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NEWS 4	Aug 08	PHARMAMarketLetter(PHARMAML) - new on STN
NEWS 5	Aug 19	Aquatic Toxicity Information Retrieval (AQUIRE) now available on STN
NEWS 6	Aug 26	Sequence searching in REGISTRY enhanced
NEWS 7	Sep 03	JAPIO has been reloaded and enhanced
NEWS 8	Sep 16	Experimental properties added to the REGISTRY file
NEWS 9	Sep 16	CA Section Thesaurus available in CAPLUS and CA
NEWS 10	Oct 01	CASREACT Enriched with Reactions from 1907 to 1985
NEWS 11	Oct 24	BEILSTEIN adds new search fields
NEWS 12	Oct 24	Nutraceuticals International (NUTRACEUT) now available on STN
NEWS 13	Nov 18	DKILIT has been renamed APOLLIT
NEWS 14	Nov 25	More calculated properties added to REGISTRY
NEWS 15	Dec 04	CSA files on STN
NEWS 16	Dec 17	PCTFULL now covers WP/PCT Applications from 1978 to date
NEWS 17	Dec 17	TOXCENTER enhanced with additional content
NEWS 18	Dec 17	Adis Clinical Trials Insight now available on STN
NEWS 19	Jan 29	Simultaneous left and right truncation added to COMPENDEX, ENERGY, INSPEC
NEWS 20	Feb 13	CANCERLIT is no longer being updated
NEWS 21	Feb 24	METADEX enhancements
NEWS 22	Feb 24	PCTGEN now available on STN
NEWS 23	Feb 24	TEMA now available on STN
NEWS 24	Feb 26	NTIS now allows simultaneous left and right truncation
NEWS 25	Feb 26	PCTFULL now contains images
NEWS 26	Mar 04	SDI PACKAGE for monthly delivery of multifile SDI results
NEWS 27	Mar 19	APOLLIT offering free connect time in April 2003
NEWS 28	Mar 20	EVENTLINE will be removed from STN
NEWS 29	Mar 24	PATDPAFULL now available on STN
NEWS 30	Mar 24	Additional information for trade-named substances without structures available in REGISTRY
NEWS 31	Mar 24	Indexing from 1957 to 1966 added to records in CA/CAPLUS
NEWS 32	Apr 11	Display formats in DGENE enhanced
NEWS 33	Apr 14	MEDLINE Reload

NEWS EXPRESS	April 4 CURRENT WINDOWS VERSION IS V6.01a, CURRENT MACINTOSH VERSION IS V6.0b(ENG) AND V6.0Jb(JP), AND CURRENT DISCOVER FILE IS DATED 01 APRIL 2003
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NEWS LOGIN	Welcome Banner and News Items
NEWS PHONE	Direct Dial and Telecommunication Network Access to STN
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=> FIL MEDLINE BIOSIS EMBASE CA SCISEARCH
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FILE 'SCISEARCH' ENTERED AT 12:07:54 ON 14 APR 2003
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=> s (antisense or oligo?) and (conjugat? or complex?)
L1 130149 (ANTISENSE OR OLIGO?) AND (CONJUGAT? OR COMPLEX?)

=> s (antisense or oligo?) (s) (conjugat? or complex?)
L2 78619 (ANTISENSE OR OLIGO?) (S) (CONJUGAT? OR COMPLEX?)

=> s l2 and (conjuga? or complex?) (s) (somatost? or octreot?)
L3 102 L2 AND (CONJUGA? OR COMPLEX?) (S) (SOMATOST? OR OCTREOT?)

=> s l2 and (conjuga? or complex?) (5n) (somatost? or octreot?)
L4 14 L2 AND (CONJUGA? OR COMPLEX?) (5N) (SOMATOST? OR OCTREOT?)

=> dup rem l4
PROCESSING COMPLETED FOR L4
L5 10 DUP REM L4 (4 DUPLICATES REMOVED)

=> d l5 1-10 ibib abs

L5 ANSWER 1 OF 10 CA COPYRIGHT 2003 ACS
ACCESSION NUMBER: 138:29120 CA
TITLE: Preparation of peptide drug-alkylene glycol **oligomer conjugates**
INVENTOR(S): Ekwuribe, Nnochiri N.; Price, Christopher H.; Ansari, Aslam M.; Odenbaugh, Amy L.
PATENT ASSIGNEE(S): Nobex Corporation, USA
SOURCE: PCT Int. Appl., 201 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002098446	A1	20021212	WO 2002-US17567	20020604

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

BR 2001006401	A	20030211	BR 2001-6401	20011011
JP 2003104913	A2	20030409	JP 2001-317307	20011015

PRIORITY APPLN. INFO.: US 2001-873797 A 20010604
OTHER SOURCE(S): MARPAT 138:29120

AB A non-polydispersed mixt. of **conjugates** in which each **conjugate** in the mixt. comprises a peptide drug coupled to an **oligomer** that includes a polyalkylene glycol moiety is disclosed. The mixt. may exhibit higher in vivo activity than a polydispersed mixt. of similar conjugates. The mixt. may be more effective at surviving an in vitro model of intestinal digestion than polydispersed mixts. of similar conjugates. The mixt. may result in less inter-subject variability than polydispersed mixts. of similar conjugates. Thus, non-polydispersed hexaethylene glycol was treated with phosgene soln., followed by treatment with N-hydroxysuccinimide (NHS) to give give the NHS ester. Human growth hormone (Saizen) was allowed to react with the NHS ester to give the conjugate.

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 2 OF 10 CA COPYRIGHT 2003 ACS
ACCESSION NUMBER: 137:114495 CA
TITLE: Polypodal chelants for metallopharmaceuticals
INVENTOR(S): Liu, Shuang
PATENT ASSIGNEE(S): Bristol-Myers Squibb Company, USA
SOURCE: PCT Int. Appl., 94 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002055112	A2	20020718	WO 2001-US50416	20011227

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2002094316	A1	20020718	US 2001-33769	20011227

PRIORITY APPLN. INFO.: US 2001-260618P P 20010109

OTHER SOURCE(S): MARPAT 137:114495

AB Polypodal chelants are disclosed, as well as chelates of the chelates of the chelants with metal ions to form radiopharmaceutical and radioactive, MRI and X-ray or CT imaging compds. and compns. Therapeutic and imaging methods of use are also disclosed. Several examples of synthetic procedures and radiochem. purity of 111In and 153Sm complexes of the polypodal complexes are given. The chelants and complexes may be suitable as diagnostic and therapeutic agents such as for treating conditions assocd. with angiogenic neovasculature and heavy metal toxicity. They are also useful for targeting biomols.

L5 ANSWER 3 OF 10 CA COPYRIGHT 2003 ACS

ACCESSION NUMBER: 136:359644 CA

TITLE: Compositions for enhanced delivery of bioactive molecules

INVENTOR(S): Lewis, Danny; Schmidt, Paul; Hinds, Kenneth

PATENT ASSIGNEE(S): PR Pharmaceuticals, Inc., USA

SOURCE: PCT Int. Appl., 24 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002036169	A2	20020510	WO 2001-US45154	20011031
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2002020002	A5	20020515	AU 2002-20002	20011031
US 2002155158	A1	20021024	US 2001-999820	20011031

PRIORITY APPLN. INFO.: US 2000-244499P P 20001031
WO 2001-US45154 W 20011031

AB Formulations for controlled, prolonged release of bioactive mols. such as therapeutic proteins, peptides and oligonucleotides have been developed. These formulations are based on solid microparticles or nanoparticles formed of the combination of biodegradable, synthetic polymers such as poly(lactic acid) (PLA), poly(glycolic acid) (PGA), and copolymers. Bioactive mols. are coupled to hydrophilic polymers such as polyethylene glycol or polypropylene glycol and formulated to provide controlled release. The bioactive mols. are more stable, less immunogenic and have improved release rate profiles with lower burst levels and increased drug loading relative to the same bioactive mols. lacking coupled hydrophilic polymers. The controlled release formulations can be administered by injection, by inhalation, nasally, or orally. Leu-enkephalin was covalently modified with polyethylene glycol. The peptide was converted to its PEG-modified form. PEG-leu-enkephalin was dissolved in a 1:9 DMSO:PBS mixt. to a final concn. of 50 mg/mL. PLGA was dissolved in methylene chloride to a final concn. of 200 mg/mL. The primary emulsion was created by homogenizing 200 .mu.L of the peptide soln. with 3 mL of the polymer soln. at 10,000 rpm for 3 min. After the solvent had evapd. and the microparticles had hardened, they were collected by filtration and dried in vacuo before anal. The particles were characterized for core loading encapsulation efficiency, and particle size. Covalent coupling of PEG 5000 to leu-enkephalin increased the drug loading attainable from 0.07 to 0.36 % for the double emulsion technique and from 0.3 to 3.95 % for the

monophase method.

L5 ANSWER 4 OF 10 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 2002460246 MEDLINE
DOCUMENT NUMBER: 22207672 PubMed ID: 12217415
TITLE: **Antisense** peptide nucleic acids **conjugated** to **somatostatin** analogs and targeted at the n-myc oncogene display enhanced cytotoxity to human neuroblastoma IMR32 cells expressing somatostatin receptors.
AUTHOR: Sun Lichun; Fuselier Joseph A; Murphy William A; Coy David H
CORPORATE SOURCE: Department of Medicine, Peptide Research Laboratories, Tulane Health Sciences Center, Tulane University School of Medicine, 1430 Tulane Avenue, New Orleans, LA 70112-2699, USA.
SOURCE: PEPTIDES, (2002 Sep) 23 (9) 1557-65.
Journal code: 8008690. ISSN: 0196-9781.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200302
ENTRY DATE: Entered STN: 20020910
Last Updated on STN: 20030225
Entered Medline: 20030224

AB Peptide nucleic acid (PNA) sequences are synthetic versions of naturally occurring oligonucleotides which display improved binding properties to DNA and RNA, but are still poorly internalized across cell membranes. In an effort to employ the rapid binding/internalization properties of somatostatin agonist analogs and the over-expression of somatostatin receptors on many types of tumor cells, PNAs complementary to target sites throughout 5'-UTR, translation start site and coding region of the n-myc oncogene were **conjugated** to a **somatostatin** analog (SSA) with retention of high somatostatin biological potency. IMR32 cells, which over-express somatostatin receptor type 2 (SSTR2) and contain the n-myc oncogene, were treated with these PNA-SSA conjugates. The results show that PNA conjugates targeted to the 5'-UTR terminus and to regions at or close to the translation start site could effectively inhibit n-myc gene expression and cell growth, whereas the non-conjugate PNAs were without effect at similar doses. The most potent inhibition of cell growth was achieved with PNAs binding to the translation start site, but those complementary to the middle coding region or middle upstream site between 5'-UTR and translation start site displayed no inhibition of gene expression. These observations were extended to four other cell lines: GH3 cells which express SSTRs with the n-myc gene, SKNSH cells containing a silent n-myc gene without SSTR2, HT-29 cells carrying the c-myc but no n-myc gene, and CHO-K1 cells lacking SSTR2 with n-myc gene. The results show that there was almost no effect on these four cell lines. Our study indicates that PNAs conjugated to SSA exhibited improved inhibition of gene expression possibly due to facilitated cellular uptake of the PNAs. These **conjugates** were mRNA sequence- and SSTR2-specific suggesting that many other genes associated with tumor growth could be targeted using this approach and that SSA could be a novel and effective transportation vector for the PNA **antisense** strategy.

L5 ANSWER 5 OF 10 CA COPYRIGHT 2003 ACS
ACCESSION NUMBER: 135:190390 CA
TITLE: **Antisense oligonucleotide conjugates** with **somatostatin** analogs for treatment of tumors associated with high leves of the somatostatin receptor

INVENTOR(S): Eisenhut, Michael; Mier, Walter; Eritia, Ramon; Haberkorn, Uwe
PATENT ASSIGNEE(S): Deutsches Krebsforschungszentrum Stiftung des Oeffentlichen Rechts, Germany
SOURCE: Ger. Offen., 16 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 10006572	A1	20010823	DE 2000-10006572	20000214
EP 1129725	A2	20010905	EP 2001-103466	20010214
EP 1129725	A3	20030122		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
US 2001029035	A1	20011011	US 2001-781980	20010214

PRIORITY APPLN. INFO.: DE 2000-10006572 A 20000214

AB The present invention concerns an **oligonucleotide conjugate** between an **antisense** DNA to an essential gene and a somatostatin analog. The present invention concerns also this **oligonucleotide conjugate** contg. drug, preferably to the therapy of tumors, with which the somatostatin receptor (SSTR) is over-expressed. The antisense DNA, which may contain base analogs or a modified backbone, is preferably directed against the bcl-2 oncogene. Prepn. of **octreotide** analogs of **somatostatin** and their **conjugation** with **antisense oligonucleotides** is demonstrated.

L5 ANSWER 6 OF 10 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:392840 BIOSIS
DOCUMENT NUMBER: PREV200100392840
TITLE: Synthesis and labeling of peptide nucleic acid **oligomers conjugated** to **octreotate.**
AUTHOR(S): Mier, W. (1); Eritja, R.; Mohammed, A. (1); Haberkorn, U. (1); Eisenhut, M.
CORPORATE SOURCE: (1) Department of Nuclear Medicine, Universitaetsklinikum Heidelberg, 69120, Heidelberg Germany
SOURCE: Journal of Labelled Compounds and Radiopharmaceuticals, (May, 2001) Vol. 44, No. Supplement 1, pp. S954-S956. print.
Meeting Info.: Fourteenth International Symposium on Radiopharmaceutical Chemistry Interlaken, Switzerland June 10-15, 2001
ISSN: 0362-4803.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

L5 ANSWER 7 OF 10 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:300098 BIOSIS
DOCUMENT NUMBER: PREV200100300098
TITLE: Tumor-targeting peptide-**oligonucleotide conjugates.**
AUTHOR(S): Mier, W. (1); Eritja, R. (1); Mohammed, A. (1); Haberkorn, U. (1); Eisenhut, M. (1)
CORPORATE SOURCE: (1) Nuclear Medicine, Universitaetsklinikum Heidelberg, Heidelberg Germany
SOURCE: Journal of Cancer Research and Clinical Oncology, (2001) Vol. 127, No. Supplement 1, pp. S44. print.

Meeting Info.: Eleventh Congress of the Division of Experimental Cancer Research of the German Cancer Society Heidelberg, Germany April 04-06, 2001 German Cancer Society . ISSN: 0171-5216.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

L5 ANSWER 8 OF 10 CA COPYRIGHT 2003 ACS
ACCESSION NUMBER: 134:76386 CA
TITLE: Amphiphilic drug-**oligomer conjugates** with hydrolyzable lipophile components and methods for making and using the same
INVENTOR(S): Ekwuribe, Nnochiri; Ramaswamy, Muthukumar; Rajagopalan, Jayanthi
PATENT ASSIGNEE(S): Protein Delivery, Inc., USA
SOURCE: PCT Int. Appl., 69 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000078302	A1	20001228	WO 2000-US16879	20000619
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6309633	B1	20011030	US 1999-336548	19990619
BR 2000011772	A	20020402	BR 2000-11772	20000619
EP 1196157	A1	20020417	EP 2000-942956	20000619
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2003502364	T2	20030121	JP 2001-504366	20000619
NO 2001006143	A	20020218	NO 2001-6143	20011217

PRIORITY APPLN. INFO.: US 1999-336548 A 19990619
WO 2000-US16879 W 20000619

AB The present invention relates generally to hydrolyzable drug-**oligomer conjugates**, pharmaceutical compns. comprising such **conjugates**, and to methods for making and using such **conjugates** and pharmaceutical compns. For example, a conjugate of insulin, PEG, and oleic acid was prepd. and can be orally administered.
REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 9 OF 10 CA COPYRIGHT 2003 ACS
ACCESSION NUMBER: 134:21520 CA
TITLE: Novel cyanine and indocyanine dye bioconjugates for biomedical applications
INVENTOR(S): Achilefu, Samuel; Dorshow, Richard Bradley; Bugaj, Joseph Edward; Rajagopalan, Raghavan
PATENT ASSIGNEE(S): Mallinckrodt Inc., USA
SOURCE: PCT Int. Appl., 38 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000071162	A2	20001130	WO 2000-US11060	20000426
WO 2000071162	A3	20010705		
W: AU, CA, JP				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
US 6217848	B1	20010417	US 1999-325769	19990604
EP 1178830	A2	20020213	EP 2000-926343	20000426
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2003500367	T2	20030107	JP 2000-619463	20000426

PRIORITY APPLN. INFO.: US 1999-135060P P 19990520
US 1999-325769 A 19990604
WO 2000-US11060 W 20000426

OTHER SOURCE(S): MARPAT 134:21520

AB Dye-peptide conjugates useful for diagnostic imaging and therapy are disclosed. The dye-peptide conjugates include several cyanine dyes with a variety of bis- and tetrakis(carboxylic acid) homologs. The small size of the compds. allows more favorable delivery to tumor cells as compared to larger mol. wt. imaging agents. The various dyes are useful over the range of 350-1300 nm, the exact range being dependent upon the particular dye. Use of dimethylsulfoxide helps to maintain the fluorescence of the compds. The mols. of the invention are useful for diagnostic imaging and therapy, in endoscopic applications for the detection of tumors and other abnormalities and for localized therapy, for photoacoustic tumor imaging, detection and therapy, and for sonofluorescence tumor imaging, detection and therapy. For example, monooctreotate-bisethylcarboxymethyl indocyanine dye (Cytate 1) was prepd. (yield of 80%) and evaluated in the CA20948 Lewis rat model of pancreatic acinar carcinoma. Using the CCD camera, strong localization of this dye was obsd. in the tumor at 90 min post injection. At 19 h post injection the animal was again imaged and tumor visualization was easily obsd. showing specificity of this agent for somatostatin receptors present in this tumor line.

L5 ANSWER 10 OF 10 CA COPYRIGHT 2003 ACS
ACCESSION NUMBER: 129:95726 CA
TITLE: Preparation of polysaccharide-peptide derivatives with effective surface charges as radionuclide ligands
INVENTOR(S): Holmberg, Anders; Westlin, Jan-Erik; Nilsson, Sten
PATENT ASSIGNEE(S): Map Medical Technologies Oy, Finland
SOURCE: PCT Int. Appl., 40 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9828336	A1	19980702	WO 1997-FI827	19971222
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
FI 9605181	A	19980621	FI 1996-5181	19961220

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      AU 9878731         A1   19980717       AU 1998-78731     19971222
      AU 736528          B2   20010802
      EP 951478          A1   19991027       EP 1997-948934    19971222
          R:  AT, BE, CH, DE, ES, FR, IT, LI, NL, SE, IE, LT, LV, FI
      JP 2001507345      T2   20010605       JP 1998-528443    19971222
      NO 9903024         A    19990812       NO 1999-3024      19990618
      US 6455025         B1   20020924       US 1999-331405    19991018
PRIORITY APPLN. INFO.:                     FI 1996-5181      A 19961220
                                           WO 1997-FI827     W 19971222

OTHER SOURCE(S):          MARPAT 129:95726
AB    The present invention is related to polysaccharide-somatostatin-analogs
      and derivs. thereof provided with effective surface charges.  These
      compds. have remarkable therapeutic and diagnostic properties.  Thus,
      activation of dextran by oxidn. with sodium periodate, followed by
      reaction with somatostatin, taurine, and sodium cyanoborohydride gave a
      dextran-somatostatin-taurine conjugate that could be
      labeled with technetium 99m.
REFERENCE COUNT:          5     THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS
                                RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT


=> d his

     (FILE 'HOME' ENTERED AT 12:07:26 ON 14 APR 2003)

     FILE 'MEDLINE, BIOSIS, EMBASE, CA, SCISEARCH' ENTERED AT 12:07:54 ON 14
     APR 2003
L1        130149 S (ANTISENSE OR OLIGO?) AND (CONJUGAT? OR COMPLEX?)
L2         78619 S (ANTISENSE OR OLIGO?) (S) (CONJUGAT? OR COMPLEX?)
L3           102 S L2 AND (CONJUGA? OR COMPLEX?) (S) (SOMATOST? OR OCTREOT?)
L4            14 S L2 AND (CONJUGA? OR COMPLEX?) (5N) (SOMATOST? OR OCTREOT?)
L5            10 DUP REM L4 (4 DUPLICATES REMOVED)

=> s antisense or (comple? (2n) (nucleot? or oligonucl?))
   4 FILES SEARCHED...
L6       146346 ANTISENSE OR (COMPLE? (2N) (NUCLEOT? OR OLIGONUCL?))

=> s l6 and ((nucl? (3n) resist?) or degrad? or (increas? (5n) ((half (n) life) or
bioacti?)))
   4 FILES SEARCHED...
L7          6174 L6 AND ((NUCL? (3N) RESIST?) OR DEGRAD? OR (INCREAS? (5N) ((HAL
                 F (N) LIFE) OR BIOACTI?)))

=> s l7 and (((propane (n) diol) or propanediol?) and exonucl?)
L8             6 L7 AND (((PROPANE (N) DIOL) OR PROPANEDIOL?) AND EXONUCL?)

=> dup rem l8
PROCESSING COMPLETED FOR L8
L9             3 DUP REM L8 (3 DUPLICATES REMOVED)

=> d l9 1-3 ibib abs

L9   ANSWER 1 OF 3  EMBASE  COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER:   2003095019  EMBASE
TITLE:              Synthesis and properties of radiolabeled
                    CPTA-oligonucleotides.
AUTHOR:             Wagner S.; Eritja R.; Zuhayra M.; Oberdorfer F.; Mohammed
                    A.; Mier W.; Haberkorn U.; Eisenhut M.
CORPORATE SOURCE:   M. Eisenhut, Abt. Radiochem./Radiopharmak., Deutsches
                    Krebsforschungszentrum, Im Neuenheimer Feld 280, D-69120
                    Heidelberg, Germany. m.eisenhut@dkfz.de
SOURCE:             Journal of Labelled Compounds and Radiopharmaceuticals,
                    (2003) 46/2 (175-186).
```

Refs: 24
ISSN: 0362-4803 CODEN: JLCRD4
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 023 Nuclear Medicine
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB A solid phase technique for the preparation of **antisense** oligodeoxynucleotides (ODNs) is described featuring 5'-end conjugated 4-[(1,4,8,11-tetraazacyclotetradec-1-yl)-methyl]benzoic acid (CPTA). Using Fmoc-protected CPTA-C6 amidite, CPTA was conjugated to ODNs at the end of an automated DNA synthesis. To illustrate successful conjugations, the CPTA-ODNs were labeled with (99m)Tc using the stannous-chloride reduction method. The resulting (99m)Tc complexes showed differences of stability between CPTA-conjugated and CPTA-unconjugated as well as 3'-protected and 3'-unprotected ODNs. Propane-1,3-diol 3'-modification enhanced efficiently the stability of (99m)Tc labeled ODN against **exonuclease degradation**. Fmoc(3)CPTA-C6 amidite turned out to be a versatile ligand for radiometal complexation at the 5'-end. Copyright .COPYRGT. 2002 John Wiley & Sons, Ltd.

L9 ANSWER 2 OF 3 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 1998109611 MEDLINE
DOCUMENT NUMBER: 98109611 PubMed ID: 9449557
TITLE: Stability measurement of oligonucleotides in serum samples using capillary electrophoresis.
AUTHOR: Khan K; Liekens K; Van Aerschot A; Van Schepdael A; Hoogmartens J
CORPORATE SOURCE: Laboratorium voor Farmaceutische Chemie en Analyse van Geneesmiddelen, Faculteit Farmaceutische Wetenschappen, Leuven, Belgium.
SOURCE: JOURNAL OF CHROMATOGRAPHY. B, BIOMEDICAL SCIENCES AND APPLICATIONS, (1997 Nov 21) 702 (1-2) 69-76.
Journal code: 9714109. ISSN: 1387-2273.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199803
ENTRY DATE: Entered STN: 19980312
Last Updated on STN: 19980312
Entered Medline: 19980305

AB An in vitro stability study of unmodified and modified **antisense** oligonucleotides in human serum was performed with a previously developed capillary electrophoretic method using either micellar solution or entangled polymer solution depending on the oligonucleotide length to be separated. A method has been devised and validated for the extraction of oligonucleotides from serum using anion-exchange centrifugal filter units. The extracted samples were desalted by a drop dialysis method. The serum half-lives and the **degradation** patterns of unmodified and modified oligonucleotides are compared. The modified oligonucleotide used in this study is protected from **exonuclease** activity present in human serum by terminal 1,3-**propanediol** modification.

L9 ANSWER 3 OF 3 SCISEARCH COPYRIGHT 2003 ISI (R)
ACCESSION NUMBER: 1998:59276 SCISEARCH
THE GENUINE ARTICLE: YQ057
TITLE: Stability measurement of oligonucleotides in serum samples using capillary electrophoresis
AUTHOR: Khan K (Reprint); Liekens K; VanAerschot A; VanSchepdael A
CORPORATE SOURCE: FAC FARMACEUT WETENSCHAPPEN, LAB FARMACEUT CHEM & ANAL GENEESMIDDELEN, VAN EVENSTR 4, B-3000 LOUVAIN, BELGIUM

(Reprint); UNIV CATHOLIQUE LOUVAIN, REGA INST, MED CHEM LAB, B-3000 LOUVAIN, BELGIUM

COUNTRY OF AUTHOR: BELGIUM

SOURCE: JOURNAL OF CHROMATOGRAPHY B, (21 NOV 1997) Vol. 702, No. 1-2, pp. 69-76.
Publisher: ELSEVIER SCIENCE BV, PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS.
ISSN: 0378-4347.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 29

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB An in vitro stability study of unmodified and modified **antisense** oligonucleotides in human serum was performed with a previously developed capillary electrophoretic method using either micellar solution or entangled polymer solution depending on the oligonucleotide length to be separated. A method has been devised and validated for the extraction of oligonucleotides from serum using anion-exchange centrifugal filter units. The extracted samples were desalted by a drop dialysis method. The serum half-lives and the **degradation** patterns of unmodified and modified oligonucleotides are compared. The modified oligonucleotide used in this study is protected from **exonuclease** activity present in human serum by terminal 1,3-**propanediol** modification. (C) 1997 Elsevier Science B.V.

=> d his

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FILE 'MEDLINE, BIOSIS, EMBASE, CA, SCISEARCH' ENTERED AT 12:07:54 ON 14 APR 2003

L1 130149 S (ANTISENSE OR OLIGO?) AND (CONJUGAT? OR COMPLEX?)
L2 78619 S (ANTISENSE OR OLIGO?) (S) (CONJUGAT? OR COMPLEX?)
L3 102 S L2 AND (CONJUGA? OR COMPLEX?) (S) (SOMATOST? OR OCTREOT?)
L4 14 S L2 AND (CONJUGA? OR COMPLEX?) (5N) (SOMATOST? OR OCTREOT?)
L5 10 DUP REM L4 (4 DUPLICATES REMOVED)
L6 146346 S ANTISENSE OR (COMPLE? (2N) (NUCLEOT? OR OLIGONUCL?))
L7 6174 S L6 AND ((NUCL? (3N) RESIST?) OR DEGRAD? OR (INCREAS? (5N) ((
L8 6 S L7 AND (((PROPANE (N) DIOL) OR PROPANEDIOL?) AND EXONUCL?)
L9 3 DUP REM L8 (3 DUPLICATES REMOVED)

=> s l2 and ((conjugat? or complex?) (5n) (bound? or bond? or bind?) (5n) (5 or base?))
4 FILES SEARCHED...
L10 302 L2 AND ((CONJUGAT? OR COMPLEX?) (5N) (BOUND? OR BOND? OR BIND?) (5N) (5 OR BASE?))

=> s l2 and ((conjugat? or complex?) (5n) (bound? or bond? or bind?) (5n) (5 and base?))
PROXIMITY OPERATION NOT ALLOWED
PROXIMITY OPERATION NOT ALLOWED
PROXIMITY OPERATION NOT ALLOWED
PROXIMITY OPERATION NOT ALLOWED
PROXIMITY OPERATION NOT ALLOWED
Certain operators may not be nested in combination with other operators. A nested operator is valid only when it occurs at the same level or above the operator outside the nested phrase as determined by the following precedence list:

1. Numeric
2. (W), (NOTW), (A), (NOTA)

3. (S), (NOTS)
4. (P), (NOTP)
5. (L), (NOTL)
6. AND, NOT
7. OR

For example, '(MONOCLONAL(W)ANTIBOD?)(L)ANTIGEN?' is valid since (W) is above (L) on the precedence list. However, '((THIN(W)LAYER)(L)PHOSPHOLIPID#)(A)LACTONE#' is not valid since (L) is below (A) on the precedence list. The only exception is the 'OR' operator. This operator may be used in combination with any other operator. For example, '(ATOMIC OR NUCLEAR)(W)REACTOR' is valid.

```
=> s l2 and ((conjugat? or complex?) (5n) (bound? or bond? or bind?) (5n) (5))
L11         200 L2 AND ((CONJUGAT? OR COMPLEX?) (5N) (BOUND? OR BOND? OR BIND?)
                (5N) (5))

=> s l2 and ((conjugat? or complex?) (5n) (bound? or bond? or bind?) (5n) (base))
L12          68 L2 AND ((CONJUGAT? OR COMPLEX?) (5N) (BOUND? OR BOND? OR BIND?)
                (5N) (BASE))

=> d l11 and l12
L12 IS NOT VALID HERE
For an explanation, enter "HELP DISPLAY".

=> s l11 and l12
L13           5 L11 AND L12

=> dup rem l13
PROCESSING COMPLETED FOR L13
L14           2 DUP REM L13 (3 DUPLICATES REMOVED)

=> d l14 1-2 ibib abs

L14  ANSWER 1 OF 2     MEDLINE                                  DUPLICATE 1
ACCESSION NUMBER:    2001560830     MEDLINE
DOCUMENT NUMBER:     21518873   PubMed ID: 11606126
TITLE:               Inhibition of cancer cell growth by ruthenium(II) arene
                     complexes.
AUTHOR:              Morris R E; Aird R E; Murdoch P del S; Chen H; Cummings J;
                     Hughes N D; Parsons S; Parkin A; Boyd G; Jodrell D I;
                     Sadler P J
CORPORATE SOURCE:    Department of Chemistry, University of Edinburgh, West
                     Mains Road, Edinburgh EH9 3JJ, U.K.
SOURCE:              JOURNAL OF MEDICINAL CHEMISTRY, (2001 Oct 25) 44 (22)
                     3616-21.
                     Journal code: 9716531. ISSN: 0022-2623.
PUB. COUNTRY:        United States
DOCUMENT TYPE:       Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:            English
FILE SEGMENT:        Priority Journals
ENTRY MONTH:         200112
ENTRY DATE:          Entered STN: 20011022
                     Last Updated on STN: 20020122
                     Entered Medline: 20011204
```

AB Inhibition of the growth of the human ovarian cancer cell line A2780 by organometallic ruthenium(II) complexes of the type [(eta(6)-arene)Ru(X)(Y)(Z)], where arene is benzene or substituted benzene, X, Y, and Z are halide, acetonitrile, or isonicotinamide, or X,Y is ethylenediamine (en) or N-ethylethylenediamine, has been investigated. The X-ray crystal structures of the complexes [(eta(6)-p-cymene)Ru(en)Cl]PF(6) (5), [(eta(6)-p-cymene)RuCl(2)(isonicotinamide)] (7), and [(eta(6)-biphenyl)Ru(en)Cl]PF(6) (9) are reported. They have

"piano stool" geometries with eta(6) coordination of the arene ligand. Complexes with X,Y as a chelated en ligand and Z as a monofunctional leaving group had the highest activity. Complexes 5, 6 (the iodo analogue of 5), 9, and 10 (ethylethylenediamine analogue of 9) were as active as carboplatin. Hydrolysis of the reactive Ru-Cl **bond** in **complex 5** was detected by HPLC but was suppressed by the addition of chloride ions. **Complex 5 binds** strongly and selectively to G **bases** on DNA **oligonucleotides** to form monofunctional adducts. No inhibition of topoisomerase I or II by complexes 5, 6, or 9 was detected. These chelated Ru(II) arene complexes have potential as novel metal-based anticancer agents with a mechanism of action different from that of the Ru(III) complex currently on clinical trial.

L14 ANSWER 2 OF 2 CA COPYRIGHT 2003 ACS
ACCESSION NUMBER: 121:248777 CA
TITLE: Sequence specificity of the non-natural pyrido[2,3-d]pyrimidine nucleoside in triple helix formation
AUTHOR(S): Staubli, Andrea B.; Dervan, Peter B.
CORPORATE SOURCE: Beckman Inst., California Inst. Technology, Pasadena, CA, 91125, USA
SOURCE: Nucleic Acids Research (1994), 22(13), 2637-42
CODEN: NARHAD; ISSN: 0305-1048
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The non-natural pyrido[2,3-d]pyrimidine nucleoside F, which pairs preferentially with guanine (G) and adenine (A) within double-helical DNA, recognizes with high selectivity AT base pairs within triple-helical complexes. These observations suggest that F may exist in different tautomeric forms within double-helical and triple-helical complexes. Anal. of the base stacking properties of this extended ring system using two **oligodeoxyribonucleotides** contg. terminal thymines and/or pyrido[2,3-d]pyrimidines bound to adjacent sites showed a decrease in free energy of **binding** in a triple-helical **complex** in the order (**5**'-3') TT > FT > TF > FF.

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L1 130149 S (ANTISENSE OR OLIGO?) AND (CONJUGAT? OR COMPLEX?)
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L3 102 S L2 AND (CONJUGA? OR COMPLEX?) (S) (SOMATOST? OR OCTREOT?)
L4 14 S L2 AND (CONJUGA? OR COMPLEX?) (5N) (SOMATOST? OR OCTREOT?)
L5 10 DUP REM L4 (4 DUPLICATES REMOVED)
L6 146346 S ANTISENSE OR (COMPLE? (2N) (NUCLEOT? OR OLIGONUCL?))
L7 6174 S L6 AND ((NUCL? (3N) RESIST?) OR DEGRAD? OR (INCREAS? (5N) ((
L8 6 S L7 AND (((PROPANE (N) DIOL) OR PROPANEDIOL?) AND EXONUCL?)
L9 3 DUP REM L8 (3 DUPLICATES REMOVED)
L10 302 S L2 AND ((CONJUGAT? OR COMPLEX?) (5N) (BOUND? OR BOND? OR BIN
L11 200 S L2 AND ((CONJUGAT? OR COMPLEX?) (5N) (BOUND? OR BOND? OR BIN
L12 68 S L2 AND ((CONJUGAT? OR COMPLEX?) (5N) (BOUND? OR BOND? OR BIN
L13 5 S L11 AND L12
L14 2 DUP REM L13 (3 DUPLICATES REMOVED)

=> s l10 and (conjugat? (5n) (attach? or bond? or bound? or bind?) (5n) 5)
L15 70 L10 AND (CONJUGAT? (5N) (ATTACH? OR BOND? OR BOUND? OR BIND?) (5N) 5)

=> s l10 and (conjugat? (2n) (attach? or bond? or bound? or bind?) (2n) 5)
L16 22 L10 AND (CONJUGAT? (2N) (ATTACH? OR BOND? OR BOUND? OR BIND?) (2N) 5)

=> dup rem l16
PROCESSING COMPLETED FOR L16
L17 8 DUP REM L16 (14 DUPLICATES REMOVED)

=> d l17 1-8 ibib abs

L17 ANSWER 1 OF 8 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.DUPLICATE 1
ACCESSION NUMBER: 2002319091 EMBASE
TITLE: A new and efficient method for synthesis of 5'-**conjugates** of **oligonucleotides** through amide-**bond** formation on solid phase.
AUTHOR: Kachalova A.V.; Stetsenko D.A.; Romanova E.A.; Tashlitsky V.N.; Gait M.J.; Oretskaya T.S.
CORPORATE SOURCE: T.S. Oretskaya, Chemistry Department, A. N. B. Inst. of Phys.-Chem. Biol., M. V. Lomonosov Moscow State Univ., Moscow 119992, Russian Federation. oretskaya@belozersky.msu.ru
SOURCE: Helvetica Chimica Acta, (2002) 85/8 (2409-2416). Refs: 26
ISSN: 0018-019X CODEN: HCACAV
COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
AB An efficient method for synthesis of **oligonucleotide 5'-conjugates** through amide-**bond** formation on solid phase is described. Protected **oligonucleotides** containing a 5'-carboxylic acid function were obtained by use of a novel non-nucleosidic phosphoramidite building block, where the carboxylic acid moiety was protected by a 2-chlorotrityl group. The protecting group is stable to the phosphoramidite coupling conditions used in solid-phase **oligonucleotide** assembly, but is easily deprotected by mild acidic treatment. The protecting group may be removed also by ammonolysis. 5'-Carboxylate-modified **oligonucleotides** were efficiently **conjugated** on solid support under normal peptide-coupling conditions to various amines or to the N-termini of small peptides to yield products of high purity. The method is well-suited in principle for the synthesis of peptide-**oligonucleotide conjugates** containing an amide linkage between the 5'-end of an **oligonucleotide** and the N-terminus of a peptide.

L17 ANSWER 2 OF 8 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2000:366840 BIOSIS
DOCUMENT NUMBER: PREV200000366840
TITLE: Synthesis of **oligonucleotide conjugates** in anhydrous dimethyl sulfoxide.
AUTHOR(S): Milesi, David (1); Kutyavin, Igor; Lukhtanov, Eugene A.; Gorn, Vladimir V.; Reed, Michael W.
CORPORATE SOURCE: (1) Epoch Pharmaceuticals, Inc., Redmond, WA, 98052 USA
SOURCE: Phillips, M. Ian. Methods in Enzymology, (2000) Vol. 313, pp. 164-173. Methods in Enzymology; Antisense technology, Part A: General methods, methods of delivery, and RNA studies. print.
Publisher: Academic Press Inc. 525 B Street, Suite 1900, San Diego, CA, 92101-4495, USA.
ISSN: 0076-6879. ISBN: 0-12-182214-1 (cloth).
DOCUMENT TYPE: Book
LANGUAGE: English

SUMMARY LANGUAGE: English

L17 ANSWER 3 OF 8 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 1998108021 MEDLINE
DOCUMENT NUMBER: 98108021 PubMed ID: 9443977
TITLE: Solution structure of a highly stable DNA duplex conjugated to a minor groove binder.
AUTHOR: Kumar S; Reed M W; Gamper H B Jr; Gorn V V; Lukhtanov E A; Foti M; West J; Meyer R B Jr; Schweitzer B I
CORPORATE SOURCE: Walt Disney Memorial Cancer Institute at Florida Hospital, 12722 Research Parkway, Orlando, FL 32826, USA.
SOURCE: NUCLEIC ACIDS RESEARCH, (1998 Feb 1) 26 (3) 831-8. Journal code: 0411011. ISSN: 0305-1048.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199803
ENTRY DATE: Entered STN: 19980319
Last Updated on STN: 19980319
Entered Medline: 19980312

AB The tripeptide 1,2-dihydro-(3 H)-pyrrolo[3,2- e]indole-7-carboxylate (CDPI3) binds to the minor groove of DNA with high affinity. When this minor groove **binder** is **conjugated** to the **5** '-end of short **oligonucleotides** the **conjugates** form unusually stable hybrids with complementary DNA and thus may have useful diagnostic and/or therapeutic applications. In order to gain an understanding of the structural interactions between the CDPI3minor groove binding moiety and the DNA, we have determined and compared the solution structure of a duplex consisting of **oligodeoxyribonucleotide** 5'-TGATTATCTG-3' **conjugated** at the 5'-end to CDPI3 and its complementary strand to an unmodified control duplex of the same sequence using nuclear magnetic resonance techniques. Thermal denaturation studies indicated that the hybrid of this conjugate with its complementary strand had a melting temperature that was 30 degrees C higher compared with the unmodified control duplex. Following restrained molecular dynamics and relaxation matrix refinement, the solution structure of the CDPI3-conjugated DNA duplex demonstrated that the overall shape of the duplex was that of a straight B-type helix and that the CDPI3moiety was bound snugly in the minor groove, where it was stabilized by extensive van der Waal's interactions.

L17 ANSWER 4 OF 8 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 97331053 MEDLINE
DOCUMENT NUMBER: 97331053 PubMed ID: 9185578
TITLE: Efficient priming of PCR with short **oligonucleotides conjugated** to a minor groove binder.
AUTHOR: Afonina I; Zivarts M; Kutyavin I; Lukhtanov E; Gamper H; Meyer R B
CORPORATE SOURCE: Epoch Pharmaceuticals Inc., 1725 220th Street SE, #104 Bothell, WA 98021, USA.. iafonina@epochpharm.com
CONTRACT NUMBER: GM 52774 (NIGMS)
SOURCE: NUCLEIC ACIDS RESEARCH, (1997 Jul 1) 25 (13) 2657-60. Journal code: 0411011. ISSN: 0305-1048.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199707
ENTRY DATE: Entered STN: 19970812
Last Updated on STN: 19970812
Entered Medline: 19970728

AB The tripeptide 1,2-dihydro-(3H)-pyrrolo[3,2-e]indole-7-carboxylate (CDPI3) binds to the minor groove of DNA with high affinity. When this minor groove **binder** (MGB) is **conjugated** to the **5**'-end of short **oligodeoxynucleotides** (ODNs), the **conjugates** form unusually stable hybrids with complementary DNA in which the tethered CDPI3group resides in the minor groove. We show that these conjugates can be used as PCR primers. Due to their unusually high binding affinity, conjugates as short as 8-10mers can be used to amplify DNA with good specificity and efficiency. The reduced length primers described here might be appropriate for the PCR amplification of viral sequences which possess a high degree of variability (e.g., HPV, HIV) or for recent techniques such as gene hunting and differential display which amplify multiple sequences using short primer pairs.

L17 ANSWER 5 OF 8 CA COPYRIGHT 2003 ACS
ACCESSION NUMBER: 124:185540 CA
TITLE: Heparin-binding growth factors for gene therapy and anterior eye disorders
INVENTOR(S): Sosnowski, Barbara A.; Baird, J. Andrew; Houston, L. L.; Nova, Michael P.
PATENT ASSIGNEE(S): Prizm Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 204 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9524928	A2	19950921	WO 1995-US3448	19950315
WO 9524928	A3	19951012		
W: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LV, MD, MG, MN, MW, MX, NO, NZ, PL, RO, RU, SD, SI, SK, TJ, TT, UA, UZ, VN				
RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2185671	AA	19950921	CA 1995-2185671	19950315
AU 9522724	A1	19951003	AU 1995-22724	19950315
AU 702323	B2	19990218		
EP 776218	A2	19970604	EP 1995-916103	19950315
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
JP 09510352	T2	19971021	JP 1995-524212	19950315
EP 1188448	A2	20020320	EP 2001-125266	19950315
EP 1188448	A3	20020417		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE				

PRIORITY APPLN. INFO.:
US 1994-213446 A 19940315
US 1994-213447 A 19940315
EP 1995-916103 A3 19950315
WO 1995-US3448 W 19950315

AB Conjugates of a heparin-binding growth factor (e.g. an FGF receptor-binding protein), a linker, and a targeted active agent are provided for prevention of recurrence of pterygii, closure of trabeculectomy, and corneal hazing following excimer laser surgery. The linker is selected to increase the specificity, toxicity, soly., serum stability, and/or intracellular availability of the targeted moiety. Several linkers may be included to take advantage of desired properties of each linker. The area of the eye that was surgically treated is contacted with the conjugate during or immediately after surgery.
Conjugates of a heparin-binding growth factor and a nucleic-acid binding domain are provided which bind nucleic acid mols. and may be used to deliver nucleic acid encoding a cytotoxic protein or an

antisense nucleic acid to cells expressing receptors for the heparin-binding growth factor. Thus, recombinant saporin (a cytotoxic ribosome-inactivating protein from leaves of Saponaria officinalis) was produced in Escherichia coli as a fusion protein with FGF which had an IC50 of 0.6 nM toward human melanoma cells.

L17 ANSWER 6 OF 8 CA COPYRIGHT 2003 ACS
ACCESSION NUMBER: 124:166374 CA
TITLE: Cleavage of double-stranded DNA by 'metalloporphyrin-linker-oligonucleotide' molecules: influence of the linker
AUTHOR(S): Bigey, Pascal; Pratviel, Genevieve; Meunier, Bernard
CORPORATE SOURCE: Lab. Chimie Coordination CNRS, Toulouse, 31077, Fr.
SOURCE: Nucleic Acids Research (1995), 23(19), 3894-900
CODEN: NARHAD; ISSN: 0305-1048
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Manganese porphyrin-linker-triple-helix-forming oligonucleotide mols. were prepd. and their ability to cleave in vitro a double-stranded DNA target present in the HIV-1 genome was studied. The nature of the linker is a detg. factor of the cleavage efficiency. Cleavage yields as high as 80% were obsd. when the linker was a spermine residue and in the absence of a large excess of free spermine known to stabilize triplex structures. The hydrophobic nature of aliph. diamine linker modified the cleaver-DNA interactions and reduced the efficiency of DNA cleavage.

L17 ANSWER 7 OF 8 MEDLINE DUPLICATE 4
ACCESSION NUMBER: 96035873 MEDLINE
DOCUMENT NUMBER: 96035873 PubMed ID: 7556188
TITLE: **Antisense** effects of cholesterol-**oligodeoxynucleotide conjugates** associated with poly(alkylcyanoacrylate) nanoparticles.
AUTHOR: Godard G; Boutorine A S; Saison-Behmoaras E; Helene C
CORPORATE SOURCE: Laboratoire de Biophysique, INSERM U201, CNRS URA481, Museum National d'Histoire Naturelle, Paris, France.
SOURCE: EUROPEAN JOURNAL OF BIOCHEMISTRY, (1995 Sep 1) 232 (2) 404-10.
Journal code: 0107600. ISSN: 0014-2956.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199511
ENTRY DATE: Entered STN: 19951227
Last Updated on STN: 19970203
Entered Medline: 19951114

AB Oligonucleotides covalently attached to a cholesteryl moiety are more stable in biological media and better taken up by eukaryotic cells. However, their anchoring in hydrophobic cellular membranes and endosomes after endocytosis restricts their access to cellular nucleic acids. New methods of cellular delivery and the biological activity of the conjugates were studied. The cholesteryl residue was **conjugated** via disulfide **bond** to the **5'** or 3' terminal phosphate group of two **oligodeoxyribonucleotide** dodecamers complementary to the mutated region of Ha-ras oncogene mRNA. The conjugates were able to form complementary duplexes with the mutated 27-b target fragment of mRNA but not with the wild-type sequence. Efficient sequence-specific RNase H cleavage of complementary mRNA was induced with low (< or = 500 nM) concentrations of the conjugates. At higher concentrations, this cleavage was progressively inhibited, probably due to an interaction between RNase H and the cholesterol residue. The hydrophobic conjugates could be adsorbed onto poly(isohexylcyanoacrylate) nanoparticles via their

cholesteryl moieties and delivered to eukaryotic cells. Cholesterol-**conjugated oligonucleotides** were able to sequence-specifically inhibit the proliferation of T24 human bladder carcinoma cells in culture.

L17 ANSWER 8 OF 8 CA COPYRIGHT 2003 ACS
ACCESSION NUMBER: 99:176494 CA
TITLE: Isomerizing isolated to **conjugated** double bonds in **oligodienes**
INVENTOR(S): Kampf, Wolfgang; Herrmann, Christoph
PATENT ASSIGNEE(S): Chemische Werke Huels A.-G. , Fed. Rep. Ger.
SOURCE: Ger. Offen., 26 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 3205990	A1	19830901	DE 1982-3205990	19820219
EP 86894	A1	19830831	EP 1982-111787	19821218
R: AT, BE, CH, DE, FR, GB, IT, LI, NL, SE				
JP 58152006	A2	19830909	JP 1983-23889	19830217
CA 1199037	A1	19860107	CA 1983-421854	19830217
US 4556754	A	19851203	US 1983-467978	19830218

PRIORITY APPLN. INFO.:
DE 1982-3205990 19820219
DE 1982-3227684 19820724
DE 1982-3227685 19820724

AB The title reaction is carried out in the presence of KOH, RbOH, or CsOH and alcs., or Li or Na alkoxides and K, Rb, or Cs salts, at 80-220.degree. in inert atms. Thus, when 200 g polybutadiene [9003-17-2] (mol. wt. 1500, cis-1,4 content 76%, **conjugated** double **bond** content <0.**5**%) was heated with 16 g tert-BuOH [75-65-0] and 4 g powd. KOH under Ar at 180.degree. for 2,3, and 4 h, the content of conjugated diolefins was 11.6, 15.0, and 26.0; conjugated triolefins 0.07, 0.08, and 0.12; and conjugated tetraolefins 0.02, 0.03, and 0.04%, resp. A 50-.mu. film of isomerized polymer on sheet metal was dust dry and thoroughly dry (DIN 53 150) after 1.5 and 2 h, resp., compared with 7 h for unisomerized polymer.

=> d his

(FILE 'HOME' ENTERED AT 12:07:26 ON 14 APR 2003)

FILE 'MEDLINE, BIOSIS, EMBASE, CA, SCISEARCH' ENTERED AT 12:07:54 ON 14 APR 2003

L1 130149 S (ANTISENSE OR OLIGO?) AND (CONJUGAT? OR COMPLEX?)
L2 78619 S (ANTISENSE OR OLIGO?) (S) (CONJUGAT? OR COMPLEX?)
L3 102 S L2 AND (CONJUGA? OR COMPLEX?) (S) (SOMATOST? OR OCTREOT?)
L4 14 S L2 AND (CONJUGA? OR COMPLEX?) (5N) (SOMATOST? OR OCTREOT?)
L5 10 DUP REM L4 (4 DUPLICATES REMOVED)
L6 146346 S ANTISENSE OR (COMPLE? (2N) (NUCLEOT? OR OLIGONUCL?))
L7 6174 S L6 AND ((NUCL? (3N) RESIST?) OR DEGRAD? OR (INCREAS? (5N) ((
L8 6 S L7 AND (((PROPANE (N) DIOL) OR PROPANEDIOL?) AND EXONUCL?)
L9 3 DUP REM L8 (3 DUPLICATES REMOVED)
L10 302 S L2 AND ((CONJUGAT? OR COMPLEX?) (5N) (BOUND? OR BOND? OR BIN
L11 200 S L2 AND ((CONJUGAT? OR COMPLEX?) (5N) (BOUND? OR BOND? OR BIN
L12 68 S L2 AND ((CONJUGAT? OR COMPLEX?) (5N) (BOUND? OR BOND? OR BIN
L13 5 S L11 AND L12
L14 2 DUP REM L13 (3 DUPLICATES REMOVED)
L15 70 S L10 AND (CONJUGAT? (5N) (ATTACH? OR BOND? OR BOUND? OR BIND?)

```
L16          22 S L10 AND (CONJUGAT? (2N) (ATTACH? OR BOND? OR BOUND? OR BIND?)
L17           8 DUP REM L16 (14 DUPLICATES REMOVED)

=> s l11 and (conjugat? (5n) (attach? or bond? or bound? or bind?) (5n) (base)
UNMATCHED LEFT PARENTHESIS 'AND (CONJUGAT?'
The number of right parentheses in a query must be equal to the
number of left parentheses.

=> s l11 and (conjugat? (5n) (attach? or bond? or bound? or bind?) (5n) (base))
L18          0 L11 AND (CONJUGAT? (5N) (ATTACH? OR BOND? OR BOUND? OR BIND?)
               (5N) (BASE))

=> s l11 and (conjugat? (5n) (attach? or bond? or bound? or bind?) (s) (base))
L19          2 L11 AND (CONJUGAT? (5N) (ATTACH? OR BOND? OR BOUND? OR BIND?)
               (S) (BASE))

=> dup rem l19
PROCESSING COMPLETED FOR L19
L20          1 DUP REM L19 (1 DUPLICATE REMOVED)

=> d l20 ibib abs

L20  ANSWER 1 OF 1     MEDLINE                                  DUPLICATE 1
ACCESSION NUMBER:    1998064946     MEDLINE
DOCUMENT NUMBER:     98064946   PubMed ID: 9414402
TITLE:               Comparison of triple helix formation by polypurine versus
                     polypyrimidine oligodeoxynucleotides when
                     conjugated to a DNA intercalator.
AUTHOR:              Orson F M; Klysik J; Glass G A; Kinsey B M
CORPORATE SOURCE:    Veterans Affairs Medical Center Research Center on AIDS and
                     HIV Infections, Houston, TX, USA.
CONTRACT NUMBER:     AI28071 (NIAID)
     NS32583 (NINDS)
SOURCE:              JOURNAL OF EXPERIMENTAL THERAPEUTICS AND ONCOLOGY, (1996
                     May) 1 (3) 177-85.
                     Journal code: 9604933. ISSN: 1359-4117.
PUB. COUNTRY:        ENGLAND: United Kingdom
DOCUMENT TYPE:       Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:            English
FILE SEGMENT:        Priority Journals
ENTRY MONTH:         199801
ENTRY DATE:          Entered STN: 19980217
                     Last Updated on STN: 19980217
                     Entered Medline: 19980130
```

AB Biological applications of triplex forming oligonucleotides will require the development of oligomers with high avidity and specificity. We examined the **binding** enhancement resulting from intercalator **conjugation** to both parallel design (polythymidine T15) and antiparallel design (polypurine AG15, for binding a 15 **base** pair polypurine-polypyrimidine sequence in the IL-2R alpha gene enhancer) **oligomers** under various ionic strength and temperature conditions. **Oligonucleotides** were **conjugated** through a urea link to 6,9 diamino-3-methoxy acridine (to give T15C and AG15C). Intercalator **conjugation** dramatically enhanced the specific triplex **binding** avidity (Kd = **5** nM for AG15C and 275 nM for T15C at 25 degrees C, compared to 2 microM for AG15 and > 50 microM for T15 at 25 degrees C), without detectable binding to an inappropriate target sequence. Surprisingly, triplex formation with AG15C occurred at lower Mg2+ concentrations than with T15C. AG15 and AG15C showed rapid Mg2+ dependent self association, but not T15C or T15. T15C triplex formation occurred rapidly (completion in less than 4 min), while AG15C bound to its target sequence more slowly over 20-24 h. Thus, binding constants in the low nanomolar range are now achievable with intercalator

conjugated polypurine antiparallel binding **oligonucleotides**, a prerequisite for biological applications of such agents.

=> s l11 and (conjugat? (5n) (attach? or bond? or bound? or bind?) (s) (link? or alkyl?))
<------User Break------>

(S) (LINK? OR ALKYL?))

=>
=> dhis
DHIS IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter
"HELP COMMANDS" at an arrow prompt (=>).

=> d his

(FILE 'HOME' ENTERED AT 12:07:26 ON 14 APR 2003)

FILE 'MEDLINE, BIOSIS, EMBASE, CA, SCISEARCH' ENTERED AT 12:07:54 ON 14 APR 2003

```
L1       130149 S (ANTISENSE OR OLIGO?) AND (CONJUGAT? OR COMPLEX?)
L2        78619 S (ANTISENSE OR OLIGO?) (S) (CONJUGAT? OR COMPLEX?)
L3          102 S L2 AND (CONJUGA? OR COMPLEX?) (S) (SOMATOST? OR OCTREOT?)
L4           14 S L2 AND (CONJUGA? OR COMPLEX?) (5N) (SOMATOST? OR OCTREOT?)
L5           10 DUP REM L4 (4 DUPLICATES REMOVED)
L6       146346 S ANTISENSE OR (COMPLE? (2N) (NUCLEOT? OR OLIGONUCL?))
L7         6174 S L6 AND ((NUCL? (3N) RESIST?) OR DEGRAD? OR (INCREAS? (5N) ((
L8            6 S L7 AND (((PROPANE (N) DIOL) OR PROPANEDIOL?) AND EXONUCL?)
L9            3 DUP REM L8 (3 DUPLICATES REMOVED)
L10         302 S L2 AND ((CONJUGAT? OR COMPLEX?) (5N) (BOUND? OR BOND? OR BIN
L11         200 S L2 AND ((CONJUGAT? OR COMPLEX?) (5N) (BOUND? OR BOND? OR BIN
L12          68 S L2 AND ((CONJUGAT? OR COMPLEX?) (5N) (BOUND? OR BOND? OR BIN
L13           5 S L11 AND L12
L14           2 DUP REM L13 (3 DUPLICATES REMOVED)
L15          70 S L10 AND (CONJUGAT? (5N) (ATTACH? OR BOND? OR BOUND? OR BIND?)
L16          22 S L10 AND (CONJUGAT? (2N) (ATTACH? OR BOND? OR BOUND? OR BIND?)
L17           8 DUP REM L16 (14 DUPLICATES REMOVED)
L18           0 S L11 AND (CONJUGAT? (5N) (ATTACH? OR BOND? OR BOUND? OR BIND?)
L19           2 S L11 AND (CONJUGAT? (5N) (ATTACH? OR BOND? OR BOUND? OR BIND?)
L20           1 DUP REM L19 (1 DUPLICATE REMOVED)
L21          24 S L11 AND (CONJUGAT? (5N) (ATTACH? OR BOND? OR BOUND? OR BIND?)
```

=> dup rem l21
PROCESSING COMPLETED FOR L21
L22 12 DUP REM L21 (12 DUPLICATES REMOVED)

=> d l22 1-12 ibib abs

L22 ANSWER 1 OF 12 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.DUPLICATE 1
ACCESSION NUMBER: 2002319091 EMBASE
TITLE: A new and efficient method for synthesis of **5'-conjugates** of **oligonucleotides** through amide-**bond** formation on solid phase.
AUTHOR: Kachalova A.V.; Stetsenko D.A.; Romanova E.A.; Tashlitsky V.N.; Gait M.J.; Oretskaya T.S.
CORPORATE SOURCE: T.S. Oretskaya, Chemistry Department, A. N. B. Inst. of Phys.-Chem. Biol., M. V. Lomonosov Moscow State Univ., Moscow 119992, Russian Federation.
oretskaya@belozersky.msu.ru

SOURCE: Helvetica Chimica Acta, (2002) 85/8 (2409-2416).
Refs: 26
ISSN: 0018-019X CODEN: HCACAV
COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English

AB An efficient method for synthesis of **oligonucleotide 5'-conjugates** through amide-**bond** formation on solid phase is described. Protected **oligonucleotides** containing a 5'-carboxylic acid function were obtained by use of a novel non-nucleosidic phosphoramidite building block, where the carboxylic acid moiety was protected by a 2-chlorotrityl group. The protecting group is stable to the phosphoramidite coupling conditions used in solid-phase **oligonucleotide** assembly, but is easily deprotected by mild acidic treatment. The protecting group may be removed also by ammonolysis. 5'-Carboxylate-modified **oligonucleotides** were efficiently **conjugated** on solid support under normal peptide-coupling conditions to various amines or to the N-termini of small peptides to yield products of high purity. The method is well-suited in principle for the synthesis of peptide-**oligonucleotide conjugates** containing an amide **linkage** between the 5'-end of an **oligonucleotide** and the N-terminus of a peptide.

L22 ANSWER 2 OF 12 SCISEARCH COPYRIGHT 2003 ISI (R)
ACCESSION NUMBER: 2001:746385 SCISEARCH
THE GENUINE ARTICLE: 471CP
TITLE: Occurrence of oligosialic acids on integrin alpha(5) subunit and their involvement in cell adhesion to fibronectin
AUTHOR: Nadanaka S (Reprint); Sato C; Kitajima K; Katagiri K; Irie S; Yamagata T
CORPORATE SOURCE: Kyoto Univ, Grad Sch Biostudies, Sakyo Ku, 46-29 Yoshida Shimoadachi, Kyoto 6068304, Japan (Reprint); Kyoto Univ, Grad Sch Biostudies, Sakyo Ku, Kyoto 6068304, Japan; Nippi Res Inst Biomatrix, Adachi Ku, Tokyo 1208601, Japan; Nagoya Univ, Grad Sch Bioagr Sci, Dept Appl Mol Biosci, Nagoya, Aichi 4648601, Japan; Kyoto Univ, Bayer Chair Dept Mol Immunol & Allergy, Sakyo Ku, Kyoto 6068501, Japan; Japan Inst Leather Res, Div Glycobiol & Glycotechnol, Adachi Ku, Tokyo 1208601, Japan
COUNTRY OF AUTHOR: Japan
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (7 SEP 2001) Vol. 276, No. 36, pp. 33657-33664.
Publisher: AMER SOC BIOCHEMISTRY MOLECULAR BIOLOGY INC, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814 USA.
ISSN: 0021-9258.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 42

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Integrin alpha (5)beta (1), a major fibronectin receptor, functions in a wide variety of biological phenomena. We have found that alpha2-8-**linked oligosialic** acids with 5:5 degree of polymerization (DP) less than or equal to 7 occur on integrin alpha (5) subunit of the human melanoma cell line G361. The integrin alpha (5) subunit immunoprecipitated with anti-integrin alpha (5) antibody reacted with the monoclonal antibody 12E3, which recognizes **oligo**/polysialic acid with DP greater than or equal to 5 but not with the polyclonal antibody H.46 recognizing **oligo**/polysialic acid with DP greater than or equal to 8. The occurrence of **oligosialic** acids was further demonstrated by fluorometric C-7/C-9 analysis on the

immunopurified integrin alpha (5) subunit. **Oligosialic** acids were also found in the alpha (5) subunit of several other human cells such as foreskin fibroblast and chronic erythroleukemia K562 cells. These results suggest the ubiquitous modification with unique **oligosialic** acids occurs on the ar, subunit of integrin alpha (5)beta (1). The adhesion of human melanoma G361 cells to fibronectin was mainly mediated by integrin alpha (5)beta (1). Treatment of cells with sialidase from Arthrobacter ureafaciens cleaving alpha2-3-, alpha2-6-, and alpha2-8-**linked** sialic acids inhibited adhesion to fibronectin. On the other hand, N-acetyl-neuraminidase II, which cleaves alpha2-3 and alpha2-6 but not alpha2-8 **linkages**, showed no inhibitory activity. After the loss of **oligosialic** acids, integrin alpha (**5**)beta (1), failed to **bind** to fibronectin-**conjugated** Sepharose, indicating that the **oligosialic** acid on the a5 subunit of integrin alpha (5)beta (1) plays important roles in cell adhesion to fibronectin.

L22 ANSWER 3 OF 12 CA COPYRIGHT 2003 ACS
ACCESSION NUMBER: 133:346526 CA
TITLE: Binding and photoreactivity of psoralen linked to triple helix-forming oligonucleotides
AUTHOR(S): Oh, Dennis H.; Hanawalt, Philip C.
CORPORATE SOURCE: Department of Biological Sciences and Department of Dermatology, Stanford University, Stanford, CA, 94305-5020, USA
SOURCE: Photochemistry and Photobiology (2000), 72(3), 298-307
CODEN: PHCBAP; ISSN: 0031-8655
PUBLISHER: American Society for Photobiology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Triple helix-forming **oligonucleotides conjugated** to a psoralen (psoTFO) have been designed to bind to three distinct purine-rich sequences within the human interstitial collagenase (MMP1) gene. Gel mobility shift assays indicate that these psoTFO bind to and photoreact with model target DNA sequences following UV A (UVA) irradn. The dissocn. consts. for binding of the psoTFO to their targets range from 0.3 to 4 .mu.M. Psoralen monoadducts with the purine-rich target strand and interstrand crosslinks are efficiently formed on targets contg. either 5'-ApT-3' or 5'-TpA-3' sequences adjacent to the TFO binding sequence. The dependence of adduct formation on UVA dose has provided quant. ests. of the overall rate consts. for psoralen monoadduct and crosslink formation in the presence of a TFO. When psoralen is tethered to a TFO, the rate of monoadduct formation exceeds that of crosslinking for all sequences studied. This contrasts with the relatively low rate of monoadduct formation that has been reported for free psoralens, suggesting that the bound TFO facilitates the initial photochem. that generates monoadducts, but does not significantly affect interstrand crosslink formation. PsoTFO and UVA treatment inhibit DNA cleavage by a restriction endonuclease when the psoralen covalently reacts directly at the endonuclease site. The particular TFO studied do not completely inhibit endonuclease activity when they are noncovalently bound or when the covalent psoralen adduct does not coincide with the endonuclease site. Our findings confirm that TFO are capable of directing psoralen photoadducts to specific DNA targets and suggest that TFO can significantly modulate psoralen photoreactivity and DNA-protein interactions.

REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L22 ANSWER 4 OF 12 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE 2
ACCESSION NUMBER: 1998:496009 BIOSIS
DOCUMENT NUMBER: PREV199800496009

TITLE: Application of oxathiaphospholane method for the synthesis of **oligodeoxyribonucleotide** 5'-O-**conjugates**.
AUTHOR(S): Kobylanska, Anna; Okruszek, Andrzej; Stec, Wojciech J. (1)
CORPORATE SOURCE: (1) Pol. Acad. Sci., Cent. Mol. Macromol. Stud., Dep. Bioorg. Chem., Sienkiewicza 112, 90-363 Lodz Poland
SOURCE: Nucleosides & Nucleotides, (Sept.-Nov., 1998) Vol. 17, No. 9-11, pp. 1977-1982.
ISSN: 0732-8311.
DOCUMENT TYPE: Article
LANGUAGE: English

AB 2-Thiono-1,3,2-oxathiaphospholane derivatives of lipophilic alcohols including borneol, cholesterol, menthol and heptadecanol were synthesized and reacted with support-bound **oligodeoxyribonucleotides** containing free 5'-hydroxyl groups. The reaction is catalyzed by DBU and leads to **oligodeoxyribonucleotide conjugates** possessing a lipophilic alcohol residue **bound** at the **5**'-end via a phosphorothioate **linkage**.

L22 ANSWER 5 OF 12 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.DUPLICATE 3
ACCESSION NUMBER: 97270375 EMBASE
DOCUMENT NUMBER: 1997270375
TITLE: Guanine specific DNA cleavage by photoirradiation of dibenzoyldiazomethane - **Oligonucleotide conjugates**.
AUTHOR: Nakatini K.; Shirai J.; Sando S.; Saito I.
CORPORATE SOURCE: I. Saito, Department of Synthetic Chemistry, Faculty of Engineering, Kyoto University, Kyoto 606-01, Japan. saito@sbchem.kyoto-u.ac.jp
SOURCE: Journal of the American Chemical Society, (1997) 119/33 (7626-7635).
Refs: 33
ISSN: 0002-7863 CODEN: JACSAT
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 014 Radiology
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Photoirradiation of dibenzoyldiazomethane (DBDM) produced highly electrophilic benzoylketene via Wolff rearrangement. DBDM derivative possessing an aminoalkyl side chain induced a DNA cleavage selectively at guanine (G) residues upon photoirradiation and subsequent piperidine treatment. In order to devise photochemical DNA cleavers that can specifically **alkylate** a guanine residue proximal to the target sequence of long DNA fragments, a sew reagent, DBDM-OSu, which facilitates the connection of DBDM unit to various DNA **binders**, was developed. DBDM-**oligonucleotide** (ODN) **conjugates** **5** and 6 were obtained by the coupling of 5'-aminohexyl 8-mer [H2N-CH2)6-d(ACGTCAGG)-3'] and 15-mer [H2N-(CH2)6-d(ACGTCAGGTGGCACT)-3'], respectively, with DBDM-OSu in aqueous acetonitrile in the presence of sodium bicarbonate. Photoirradiation of 5 and 6 in the presence of 25-mer 5'-d(AGTGCCACCTGACGTCTG18CTCTCTC)-3' having a complementary sequence induced cross-**linking** of both **oligomers**. A distinct cleavage band at guanine residue (G18) was observed upon heating the cross-**linked oligomers** with piperidine. A similar DNA cleavage reaction of 5'-d(AGTGCCACCTGACG14TG16CG18TG20CG22-TCT)-3' having multiple guanine sites in the presence of DBDM-ODN **conjugate** 6 indicated that the most effectively cleaved site is G16. These results demonstrated that DBDM-**oligonucleotide conjugates** can serve as a new class of photonucleases that can cleave single-stranded DNA at predetermined guanine sites. Furthermore, the reagent DBDM-OSu can be used as a convenient and effective photoinducible electrophile for the

cross-**linking** or the modification of biopolymers.

L22 ANSWER 6 OF 12 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE 4

ACCESSION NUMBER: 1996:316346 BIOSIS
DOCUMENT NUMBER: PREV199699038702
TITLE: Synthesis and binding properties of oligonucleotides covalently linked to an acridine derivative: New study of the influence of the dye attachment site.
AUTHOR(S): Asseline, Ulysse; Bonfils, Edwige; Dupret, Daniel; Thuong, Nguyen T. (1)
CORPORATE SOURCE: (1) Centre Biophysique Moleculaire, CNRS, Rue Charles Sadron, 45071 Orleans Cedex 02 France
SOURCE: Bioconjugate Chemistry, (1996) Vol. 7, No. 3, pp. 369-379. ISSN: 1043-1802.
DOCUMENT TYPE: Article
LANGUAGE: English

AB 2-Methoxy-6-chloro-9-aminoacridine has been coupled via a polymethylene **linker** to various positions of an **oligonucleotide** chain: the 3'-position, using a new universal support, the 5'-position, and both 5'- and 3'-positions via a phosphate. The intercalating agent was also **linked** to the **oligonucleotide** chain via an internucleotide phosphorothiolate. The mixture of diastereoisomers was obtained as well as each pure R-p and S-p isomer. Finally, the acridine moiety was introduced to the **5**-position of the deoxyuridine. The **binding** properties of these **oligonucleotide**-acridine **conjugates** with their DNA counterparts have been studied by absorption spectroscopy.

L22 ANSWER 7 OF 12 CA COPYRIGHT 2003 ACS
ACCESSION NUMBER: 124:185540 CA
TITLE: Heparin-binding growth factors for gene therapy and anterior eye disorders
INVENTOR(S): Sosnowski, Barbara A.; Baird, J. Andrew; Houston, L. L.; Nova, Michael P.
PATENT ASSIGNEE(S): Prizm Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 204 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9524928	A2	19950921	WO 1995-US3448	19950315
WO 9524928	A3	19951012		
W: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LV, MD, MG, MN, MW, MX, NO, NZ, PL, RO, RU, SD, SI, SK, TJ, TT, UA, UZ, VN				
RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2185671	AA	19950921	CA 1995-2185671	19950315
AU 9522724	A1	19951003	AU 1995-22724	19950315
AU 702323	B2	19990218		
EP 776218	A2	19970604	EP 1995-916103	19950315
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
JP 09510352	T2	19971021	JP 1995-524212	19950315
EP 1188448	A2	20020320	EP 2001-125266	19950315
EP 1188448	A3	20020417		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE				

PRIORITY APPLN. INFO.: US 1994-213446 A 19940315

US 1994-213447 A 19940315
EP 1995-916103 A3 19950315
WO 1995-US3448 W 19950315

AB **Conjugates** of a heparin-**binding** growth factor (e.g. an FGF receptor-binding protein), a **linker**, and a targeted active agent are provided for prevention of recurrence of pterygii, closure of trabeculectomy, and corneal hazing following excimer laser surgery. The linker is selected to increase the specificity, toxicity, soly., serum stability, and/or intracellular availability of the targeted moiety. Several linkers may be included to take advantage of desired properties of each linker. The area of the eye that was surgically treated is contacted with the conjugate during or immediately after surgery.
Conjugates of a heparin-binding growth factor and a nucleic-acid binding domain are provided which bind nucleic acid mols. and may be used to deliver nucleic acid encoding a cytotoxic protein or an **antisense** nucleic acid to cells expressing receptors for the heparin-binding growth factor. Thus, recombinant saporin (a cytotoxic ribosome-inactivating protein from leaves of Saponaria officinalis) was produced in Escherichia coli as a fusion protein with FGF which had an IC50 of 0.6 nM toward human melanoma cells.

L22 ANSWER 8 OF 12 CA COPYRIGHT 2003 ACS
ACCESSION NUMBER: 124:166374 CA
TITLE: Cleavage of double-stranded DNA by 'metalloporphyrin-linker-oligonucleotide' molecules: influence of the linker
AUTHOR(S): Bigey, Pascal; Pratviel, Genevieve; Meunier, Bernard
CORPORATE SOURCE: Lab. Chimie Coordination CNRS, Toulouse, 31077, Fr.
SOURCE: Nucleic Acids Research (1995), 23(19), 3894-900
CODEN: NARHAD; ISSN: 0305-1048
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Manganese porphyrin-linker-triple-helix-forming oligonucleotide mols. were prepd. and their ability to cleave in vitro a double-stranded DNA target present in the HIV-1 genome was studied. The nature of the linker is a detg. factor of the cleavage efficiency. Cleavage yields as high as 80% were obsd. when the linker was a spermine residue and in the absence of a large excess of free spermine known to stabilize triplex structures. The hydrophobic nature of aliph. diamine linker modified the cleaver-DNA interactions and reduced the efficiency of DNA cleavage.

L22 ANSWER 9 OF 12 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE 5
ACCESSION NUMBER: 1994:295441 BIOSIS
DOCUMENT NUMBER: PREV199497308441
TITLE: Effect of derivatization of ribophosphate backbone and terminal ribophosphate groups in oligoribonucleotides on their stability and interaction with eukaryotic cells.
AUTHOR(S): Boutorine, A. S. (1); Venyaminova, A. G.; Repkova, M. N.; Sergueyeva, Z. A.; Pyshnyi, D. V.
CORPORATE SOURCE: (1) Lab. Biophys., Museum Natl. Histoire Naturelle, 43 rue Cuvier, 75231 Paris Cedex 05 France
SOURCE: Biochimie (Paris), (1994) Vol. 76, No. 1, pp. 23-32. ISSN: 0300-9084.
DOCUMENT TYPE: Article
LANGUAGE: English

AB Various derivatives of **oligoribonucleotides** were synthesized by the H-phosphonate method. Different modifications of the ribophosphate backbone were designed in order to protect the derivatives against nucleolytic enzymes present in the biological media. These modifications include coupling of fluorescein moiety to 3'-terminal ribose, 2'-O-methylation of ribose, introduction of phosphorothioate

internucleotide bonds throughout the molecule, replacement of the two last 3'-terminal phosphodiester bonds by phosphoroamidates and coupling of the last 3'-terminal nucleotide via the 3'-3'-phosphodiester bond. All modifications were tested for their effect on the stability of the derivatives against phosphodiesterase from snake venom and nucleases of the cell culture media. 2'-O-methylated **oligoribonucleotides** containing either terminal 3'-3'-**linkage** or two 3'-terminal phosphoroamidate internucleotide bonds appeared to be the most stable under the most severe conditions used. The results demonstrate a possibility to use protected **oligoribonucleotide** derivatives for experiments in vivo when the use of deoxy-analogues might be ineffective. The uptake of 2'-O-methylated derivatives and their **5**'-cholesterol **conjugates** (coupled via a disulfide **bond**) by human carcinoma cells did not differ from that of the corresponding **oligodeoxyribonucleotides**. 85% of the bound derivatives were found in the membrane-cytosolic fraction, while only 15% were found in the nuclear fraction. The **oligonucleotide** moiety of 2'-O-methyloligoribonucleotide-cholesterol **conjugate** was not translocated through the cellular membrane. After cleavage of the **linkage** between cholesterol and **oligonucleotide** by dithiothreitol the major portion of the **oligonucleotide** moiety was released into the media. The derivatives, as well as their 5'-cholesterol **conjugates**, which entered the cells, were stable and protected from action of dithiothreitol dissolved in culture media. These results demonstrate an endocytosis mechanism of penetration as observed in similar experiments using **oligodeoxyribonucleotides**.

L22 ANSWER 10 OF 12 CA COPYRIGHT 2003 ACS
ACCESSION NUMBER: 116:79858 CA
TITLE: Ligand-label conjugates which contain polyoxoanions of sulfur or phosphorus
INVENTOR(S): Bredehorst, Reinhard; Ligler, Frances S.; Kusterbeck, Anne W.; Wemhoff, Gregory A.; Vogel, Carl Wilhelm
PATENT ASSIGNEE(S): Georgetown University, USA
SOURCE: PCT Int. Appl., 63 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9116344	A1	19911031	WO 1991-US2212	19910404
W: CA, JP				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, NL, SE				
US 5106762	A	19920421	US 1990-512272	19900420

PRIORITY APPLN. INFO.: US 1990-512272 19900420

AB Ligand-label **conjugates** contain a ligand or receptor **bonded** to an **oligopeptide** of **5**-100 amino acid residues wherein .gtoreq.1 of the amino acids contains a polyoxoanion of S or P and a plurality of the amino acids are **linked** to a chemiluminescent or fluorescent label. Such conjugates are hydrophilic and exhibit very low nonspecific binding, thereby significantly increasing the signal to background ratio in, e.g. immunoassays. Kits comprise the conjugate and a binding complement of the ligand or receptor. Ligand-tetra-S-sulfonate insulin A chain-fluorescein conjugate, contg. an N-terminal dinitrophenyl group (DNP) and 3 fluorescein groups, was prepd. in 3 steps. The amt. of nonspecific **binding** of this insulin **conjugate** to immobilized anti-DNP IgG was only .apprx.1/3 that of a conjugate in which a DNP group is **linked** to fluorescein via Lys (DNP-Lys-Fl). The amt. of the insulin conjugate specifically bound to the antibody was .apprx.1.7-fold higher than that of DNP-Lys-Fl.

L22 ANSWER 11 OF 12 MEDLINE DUPLICATE 6
ACCESSION NUMBER: 87049658 MEDLINE
DOCUMENT NUMBER: 87049658 PubMed ID: 3096375
TITLE: Preparation of protein conjugates via intermolecular hydrazone linkage.
AUTHOR: King T P; Zhao S W; Lam T
CONTRACT NUMBER: AI-17021 (NIAID)
SOURCE: BIOCHEMISTRY, (1986 Sep 23) 25 (19) 5774-9.
Journal code: 0370623. ISSN: 0006-2960.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198701
ENTRY DATE: Entered STN: 19900302
Last Updated on STN: 19970203
Entered Medline: 19870109

AB Proteins can be modified at their amino groups under gentle conditions to contain an average of three to six aryl aldehyde or acyl hydrazide groups. These two types of modified proteins at about 10 microM concentration condense with each other at pH approximately **5** to form **conjugates linked** by hydrazone **bonds**. Under proper conditions **conjugates** mainly of dimers and trimers in size or, if desired, higher **oligomers** can be obtained. The conjugates can be dissociated to their individual protein components by an exchange reaction with an excess of acetyl hydrazide. The reversible hydrazone bonds of conjugates can be reduced with NaCNBH3 to give stable hydrazide bonds. The stability of protein-hydrazone conjugates was found to be significantly greater than that of the model compound, the N-acetylhydrazone of p-carboxybenzaldehyde. This difference is believed to result from the presence of multiple hydrazone linkages in protein conjugates.

L22 ANSWER 12 OF 12 MEDLINE DUPLICATE 7
ACCESSION NUMBER: 79085676 MEDLINE
DOCUMENT NUMBER: 79085676 PubMed ID: 729572
TITLE: ADP-ribosylated histone H1 from HeLa cultures. Fundamental differences to (ADP-ribose)n-histone H1 conjugates formed into vitro.
AUTHOR: Adamietz P; Bredehorst R; Hilz H
SOURCE: EUROPEAN JOURNAL OF BIOCHEMISTRY, (1978 Nov 15) 91 (2) 317-26.
Journal code: 0107600. ISSN: 0014-2956.
PUB. COUNTRY: GERMANY, WEST: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 197903
ENTRY DATE: Entered STN: 19900315
Last Updated on STN: 19970203
Entered Medline: 19790313

AB ADP-ribosylated histone H1 was isolated from intact HeLa cells grown for 24 h with[3H]-adenosine and compared with ADP-ribosylated histone H1 synthesized from [3H]NAD by isolated HeLa nuclei. Most (ADP-ribose)n-histone H1 **conjugates** formed in vivo carried single ADP-ribose units, less than one fourth of the total ADP-ribose residues being in the form of **oligomeric** or polymeric chains. (ADP-ribose)n linked to H1 in vivo was not released by neutral NH2OH to a significant extent. Alkali treatment (pH 10.5) liberated most but not all of the ADP-ribose residues which may indicate the existence of a new type of linkage so far found only in conjugates isolated from intact tissue. No ADP-ribosylated histone H1 complex of higher molecular weight ('H1

dimer') could be detected in intact cells. By contrast, isolated HeLa nuclei formed ADP-ribosylated histone H1 which contained predominantly polymeric ADP-ribose residues. The (ADP-ribose)n residues were **linked** by NH2OH-sensitive and by NH2OH-resistant, alkali (pH 10. **5**) labile **bonds**, the majority of the **conjugates** appearing in the form of the higher-molecular-weight complex. A comparison with the ADP-ribosylated non-histone proteins indicated that histone H1 formed in vivo carried less than 2.5% of the total protein-bound ADP-ribose residues and less than 1% of the protein-bound ADP-ribose synthesized in vitro.

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=> d his

     (FILE 'HOME' ENTERED AT 12:07:26 ON 14 APR 2003)

     FILE 'MEDLINE, BIOSIS, EMBASE, CA, SCISEARCH' ENTERED AT 12:07:54 ON 14
     APR 2003
L1       130149 S (ANTISENSE OR OLIGO?) AND (CONJUGAT? OR COMPLEX?)
L2        78619 S (ANTISENSE OR OLIGO?) (S) (CONJUGAT? OR COMPLEX?)
L3          102 S L2 AND (CONJUGA? OR COMPLEX?) (S) (SOMATOST? OR OCTREOT?)
L4           14 S L2 AND (CONJUGA? OR COMPLEX?) (5N) (SOMATOST? OR OCTREOT?)
L5           10 DUP REM L4 (4 DUPLICATES REMOVED)
L6       146346 S ANTISENSE OR (COMPLE? (2N) (NUCLEOT? OR OLIGONUCL?))
L7         6174 S L6 AND ((NUCL? (3N) RESIST?) OR DEGRAD? OR (INCREAS? (5N) ((
L8            6 S L7 AND (((PROPANE (N) DIOL) OR PROPANEDIOL?) AND EXONUCL?)
L9            3 DUP REM L8 (3 DUPLICATES REMOVED)
L10         302 S L2 AND ((CONJUGAT? OR COMPLEX?) (5N) (BOUND? OR BOND? OR BIN
L11         200 S L2 AND ((CONJUGAT? OR COMPLEX?) (5N) (BOUND? OR BOND? OR BIN
L12          68 S L2 AND ((CONJUGAT? OR COMPLEX?) (5N) (BOUND? OR BOND? OR BIN
L13           5 S L11 AND L12
L14           2 DUP REM L13 (3 DUPLICATES REMOVED)
L15          70 S L10 AND (CONJUGAT? (5N) (ATTACH? OR BOND? OR BOUND? OR BIND?)
L16          22 S L10 AND (CONJUGAT? (2N) (ATTACH? OR BOND? OR BOUND? OR BIND?)
L17           8 DUP REM L16 (14 DUPLICATES REMOVED)
L18           0 S L11 AND (CONJUGAT? (5N) (ATTACH? OR BOND? OR BOUND? OR BIND?)
L19           2 S L11 AND (CONJUGAT? (5N) (ATTACH? OR BOND? OR BOUND? OR BIND?)
L20           1 DUP REM L19 (1 DUPLICATE REMOVED)
L21          24 S L11 AND (CONJUGAT? (5N) (ATTACH? OR BOND? OR BOUND? OR BIND?)
L22          12 DUP REM L21 (12 DUPLICATES REMOVED)

=> s l2 and (bcl (n) 2)
L23         255 L2 AND (BCL (N) 2)

=> s l2 (s) (bcl (n) 2)
L24         184 L2 (S) (BCL (N) 2)

=> s l2 (5n) (bcl (n) 2)
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'L7  (5A) '
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'L8  (5A) '
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'L9  (5A) '
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'L10 (5A) '
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'L11 (5A) '
L25         255 L2 (5N) (BCL (N) 2)

=> s l24 and somatost?
L26           4 L24 AND SOMATOST?
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=> dup rem l26
PROCESSING COMPLETED FOR L26
L27 2 DUP REM L26 (2 DUPLICATES REMOVED)

=> d l27 ibib abs 1-2

L27 ANSWER 1 OF 2 CA COPYRIGHT 2003 ACS
ACCESSION NUMBER: 135:190390 CA
TITLE: Antisense oligonucleotide conjugates with **somatostatin** analogs for treatment of tumors associated with high leves of the **somatostatin** receptor
INVENTOR(S): Eisenhut, Michael; Mier, Walter; Eritia, Ramon; Haberkorn, Uwe
PATENT ASSIGNEE(S): Deutsches Krebsforschungszentrum Stiftung des Oeffentlichen Rechts, Germany
SOURCE: Ger. Offen., 16 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 10006572	A1	20010823	DE 2000-10006572	20000214
EP 1129725	A2	20010905	EP 2001-103466	20010214
EP 1129725	A3	20030122		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
US 2001029035	A1	20011011	US 2001-781980	20010214

PRIORITY APPLN. INFO.: DE 2000-10006572 A 20000214
AB The present invention concerns an oligonucleotide conjugate between an antisense DNA to an essential gene and a **somatostatin** analog. The present invention concerns also this oligonucleotide conjugate contg. drug, preferably to the therapy of tumors, with which the **somatostatin** receptor (SSTR) is over-expressed. The antisense DNA, which may contain base analogs or a modified backbone, is preferably directed against the bcl-2 oncogene. Prepn. of octreotide analogs of **somatostatin** and their conjugation with antisense oligonucleotides is demonstrated.

L27 ANSWER 2 OF 2 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE 1
ACCESSION NUMBER: 2001:65051 BIOSIS
DOCUMENT NUMBER: PREV200100065051
TITLE: Preparation and evaluation of tumor-targeting peptide-oligonucleotide conjugates.
AUTHOR(S): Mier, Walter (1); Eritja, Ramon; Mohammed, Ashour; Haberkorn, Uwe; Eisenhut, Michael
CORPORATE SOURCE: (1) Department of Nuclear Medicine, Universitaetsklinikum Heidelberg, INF 400, 69120, Heidelberg: walter_mier@med.uni-heidelberg.de Germany
SOURCE: Bioconjugate Chemistry, (November December, 2000) Vol. 11, No. 6, pp. 855-860. print.
ISSN: 1043-1802.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Enormous progress has been made in the development of **antisense oligodeoxynucleotides** (ODNs) as therapeutic agents inhibiting gene expression. Unfortunately, the therapeutical application of ODNs is still held back because of the low cellular uptake and the lack of specific transport into particular cells. In this paper, we report a drug-targeting

system using **somatostatin** receptors (SSTRs) which are overexpressed in various tumors. Phosphorothioate ODNs were covalently linked to Tyr3-octreotate, an analogue of **somatostatin**. The peptide was assembled by solid-phase synthesis, oxidized to form the cyclic disulfide, and subsequently derivatized with a N-terminal maleimido functionality. 5'-Thiol derivatized phosphorothioate-ODNs directed against the protooncogene **bcl-2** were **conjugated** to this maleimido-modified peptide. Binding studies revealed that the **conjugates** retain specific binding with nanomolar affinities to SSTRs (IC50-values between 1.83 and 2.52 nM). Furthermore, melting studies with complementary DNA revealed that the terminal **conjugation** of the ODNs did not significantly affect their hybridization affinity.

=> d his

(FILE 'HOME' ENTERED AT 12:07:26 ON 14 APR 2003)

FILE 'MEDLINE, BIOSIS, EMBASE, CA, SCISEARCH' ENTERED AT 12:07:54 ON 14 APR 2003

```
L1      130149 S (ANTISENSE OR OLIGO?) AND (CONJUGAT? OR COMPLEX?)
L2       78619 S (ANTISENSE OR OLIGO?) (S) (CONJUGAT? OR COMPLEX?)
L3         102 S L2 AND (CONJUGA? OR COMPLEX?) (S) (SOMATOST? OR OCTREOT?)
L4          14 S L2 AND (CONJUGA? OR COMPLEX?) (5N) (SOMATOST? OR OCTREOT?)
L5          10 DUP REM L4 (4 DUPLICATES REMOVED)
L6      146346 S ANTISENSE OR (COMPLE? (2N) (NUCLEOT? OR OLIGONUCL?))
L7        6174 S L6 AND ((NUCL? (3N) RESIST?) OR DEGRAD? OR (INCREAS? (5N) ((
L8           6 S L7 AND (((PROPANE (N) DIOL) OR PROPANEDIOL?) AND EXONUCL?)
L9           3 DUP REM L8 (3 DUPLICATES REMOVED)
L10        302 S L2 AND ((CONJUGAT? OR COMPLEX?) (5N) (BOUND? OR BOND? OR BIN
L11        200 S L2 AND ((CONJUGAT? OR COMPLEX?) (5N) (BOUND? OR BOND? OR BIN
L12         68 S L2 AND ((CONJUGAT? OR COMPLEX?) (5N) (BOUND? OR BOND? OR BIN
L13          5 S L11 AND L12
L14          2 DUP REM L13 (3 DUPLICATES REMOVED)
L15         70 S L10 AND (CONJUGAT? (5N) (ATTACH? OR BOND? OR BOUND? OR BIND?)
L16         22 S L10 AND (CONJUGAT? (2N) (ATTACH? OR BOND? OR BOUND? OR BIND?)
L17          8 DUP REM L16 (14 DUPLICATES REMOVED)
L18          0 S L11 AND (CONJUGAT? (5N) (ATTACH? OR BOND? OR BOUND? OR BIND?)
L19          2 S L11 AND (CONJUGAT? (5N) (ATTACH? OR BOND? OR BOUND? OR BIND?)
L20          1 DUP REM L19 (1 DUPLICATE REMOVED)
L21         24 S L11 AND (CONJUGAT? (5N) (ATTACH? OR BOND? OR BOUND? OR BIND?)
L22         12 DUP REM L21 (12 DUPLICATES REMOVED)
L23        255 S L2 AND (BCL (N) 2)
L24        184 S L2 (S) (BCL (N) 2)
L25        255 S L2 (5N) (BCL (N) 2)
L26          4 S L24 AND SOMATOST?
L27          2 DUP REM L26 (2 DUPLICATES REMOVED)
```

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=> dup rem 124
ENTER L# LIST OR (END):124
'124' IS NOT VALID.  VALID FILE NAMES ARE 'MEDLINE, BIOSIS, EMBASE, CA, SCISEARCH'
You have entered a file name of duplicates to keep that is not
referenced by any of the L#s specified for this DUPLICATE command.
The file names of duplicates that can be kept are listed above.
Please enter one of these file names.

=> dup rem l24
PROCESSING COMPLETED FOR L24
L28          75 DUP REM L24 (109 DUPLICATES REMOVED)

=> s l28 and Py=< 1998
   2 FILES SEARCHED...
L29          17 L28 AND PY=< 1998
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=> d l29 ibib abs 1-17

L29 ANSWER 1 OF 17 MEDLINE
ACCESSION NUMBER: 97250531 MEDLINE
DOCUMENT NUMBER: 97250531 PubMed ID: 9096387
TITLE: Resistance to apoptosis in CTLL-2 cells constitutively expressing c-Myb is associated with induction of BCL-2 expression and Myb-dependent regulation of bcl-2 promoter activity.
AUTHOR: Salomoni P; Perrotti D; Martinez R; Franceschi C; Calabretta B
CORPORATE SOURCE: Department of Microbiology and Immunology, Thomas Jefferson University, Philadelphia, PA 19107-6799, USA.
CONTRACT NUMBER: R01 CA46782 (NCI)
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, **(1997 Apr 1)** 94 (7) 3296-301.
Journal code: 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199705
ENTRY DATE: Entered STN: 19970514
Last Updated on STN: 19980206
Entered Medline: 19970508

AB c-Myb, the cellular homologue of the transforming gene of the avian myeloblastosis virus, is preferentially expressed in all hematopoietic lineages, including T and B lymphocyte lineages. In T lymphocytes, c-Myb expression appears to be required for cell cycle progression and proliferation. To further investigate the role of c-Myb in T cell proliferation and survival, interleukin (IL) 2-dependent CTLL-2 cells were transfected with a constitutively active c-myb or with a c-myb antisense construct able to down-regulate endogenous Myb levels, and the transfectants were assessed for proliferation and survival in low concentrations of IL-2 and for susceptibility to dexamethasone-induced apoptosis. Compared with control cells, CTLL-2 cells constitutively expressing c-Myb proliferate in low concentrations of IL-2 and are less susceptible to apoptosis induced by IL-2 deprivation or treatment with dexamethasone. In contrast, cells transfected with an antisense c-myb construct do not proliferate in low concentrations of IL-2 and undergo apoptosis upon IL-2 deprivation or dexamethasone treatment more rapidly than parental cells. Overexpression of c-Myb was accompanied by up-regulation of BCL-2 expression. In transient transfection assays, the murine bcl-2 promoter was efficiently transactivated by c-Myb, but such effect was observed also in cells transfected with a DNA binding-deficient c-myb construct. Moreover, in gel retardation assays, a 38-bp **oligomer** in the shortest **bcl-2** promoter segment regulated by c-Myb formed a specific **complex** with nuclear extracts from c-Myb-transfected CTLL-2 cells. Thus, these results strongly suggest that c-Myb, in addition to regulating T cell proliferation, protects T lymphocytes from apoptosis by induction of BCL-2 expression, which involves a c-Myb-dependent mechanism of promoter regulation.

L29 ANSWER 2 OF 17 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1999:56302 BIOSIS
DOCUMENT NUMBER: PREV199900056302
TITLE: Essential role of CED-4 oligomerization in CED-3 activation and apoptosis.
AUTHOR(S): Yang, Xiaolou; Chang, Howard Y.; Baltimore, David (1)
CORPORATE SOURCE: (1) Mass. Inst. Technol., Cambridge, MA 02138 USA

SOURCE: Science (Washington D C), (**Aug. 28, 1998**) Vol. 281, No. 5381, pp. 1355-1357.
ISSN: 0036-8075.
DOCUMENT TYPE: Article
LANGUAGE: English

AB Control of the activation of apoptosis is important both in development and in protection against cancer. In the classic genetic model Caenorhabditis elegans, the pro-apoptotic protein CED-4 activates the CED-3 caspase and is inhibited by the **Bcl-2** like protein CED-9. Both processes are mediated by protein-protein interaction. Facilitating the proximity of CED-3 zymogen molecules was found to induce caspase activation and cell death. CED-4 protein **oligomerized** in cells and in vitro. This **oligomerization** induced CED-3 proximity and competed with CED-4:CED-9 interaction. Mutations that abolished CED-4 **oligomerization** inactivated its ability to activate CED-3. Thus, the mechanism of control is that CED-3 in CED-3:CED-4 **complexes** is activated by CED-4 **oligomerization**, which is inhibited by binding of CED-9 to CED-4.

L29 ANSWER 3 OF 17 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1998:313799 BIOSIS
DOCUMENT NUMBER: PREV199800313799
TITLE: E1B 19K inhibits Fas-mediated apoptosis through FADD-dependent sequestration of FLICE.
AUTHOR(S): Perez, Denise; White, Eileen (1)
CORPORATE SOURCE: (1) Cent. Advanced Biotechnol. Med., Rutgers Univ., 679 Hoes Lane, Piscataway, NJ 08854 USA
SOURCE: Journal of Cell Biology, (**June 1, 1998**) Vol. 141, No. 5, pp. 1255-1266.
ISSN: 0021-9525.
DOCUMENT TYPE: Article
LANGUAGE: English

AB E1B 19K, the adenovirus **Bcl-2** homologue, is a potent inhibitor of apoptosis induced by various stimuli including Fas and tumor necrosis factor-alpha. Fas and TNFR-1 belong to a family of cytokine-activated receptors that share key components in their signaling pathways, Fas-associating protein with death domain (FADD) and FADD-like interleukin-1beta-converting enzyme (FLICE), to induce an apoptotic response. We demonstrate here that E1B 19K and Bcl-xL are able to inhibit apoptosis induced by FADD, but not FLICE. Surprisingly, apoptosis was abrogated by E1B 19K and Bcl-xL when FADD and FLICE were coexpressed. Immunofluorescence studies demonstrated that FADD expression produced large insoluble death effector filaments that may represent **oligomerized** FADD. E1B 19K expression disrupted FADD filament formation causing FADD and FLICE to relocalize to membrane and cytoskeletal structures where E1B 19K is normally localized. E1B 19K, however, does not detectably bind to FADD, nor does it inhibit FADD and FLICE from being recruited to the death-inducing signaling **complex** (DISC) when Fas is stimulated. Thus, E1B 19K may inhibit Fas-mediated cell death downstream of FADD recruitment of FLICE but upstream of FLICE activation by disrupting FADD **oligomerization** and sequestering an essential component of the DISC.

L29 ANSWER 4 OF 17 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1998:265006 BIOSIS
DOCUMENT NUMBER: PREV199800265006
TITLE: Cytotoxicity and apoptosis produced by cytochrome P450 2E1 in Hep G2 cells.
AUTHOR(S): Chen, Qi; Cederbaum, Arthur I. (1)
CORPORATE SOURCE: (1) Mount Sinai Sch. Med., Dep. Biochem., Box 1020, One Gustave L. Levy Place, New York, NY 10029 USA
SOURCE: Molecular Pharmacology, (**April, 1998**) Vol. 53, No. 4, pp. 638-648.

ISSN: 0026-895X.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Two Hep G2 subclones overexpressing CYP2E1 were established with the use of transfection and limited dilution screening techniques. The Hep G2-C12E1-43 and -47 (E47) cells (transduced Hep G2 subclones that overexpress CYP2E1) grew at a slower rate than parental Hep G2 cells or control subclones that do not express CYP2E1, but remained fully viable. When GSH synthesis was inhibited by treatment with buthionine sulfoximine, GSH levels rapidly declined in E47 cells but not control cells, which is most likely a reflection of CYP2E1-catalyzed formation of reactive oxygen species. Under these conditions of GSH depletion, cytotoxicity and apoptosis were found only with the E47 cells. Low levels of lipid peroxidation were found in the E47 cells, which became more pronounced after GSH depletion. The antioxidants vitamin E, vitamin C, or trolox prevented the lipid peroxidation as well as the cytotoxicity and apoptosis, as did transfection with plasmid containing **antisense** CYP2E1 or overexpression of **Bcl-2**. Levels of ATP were lower in E47 cells because of damage to mitochondrial **complex** 1. When GSH was depleted, oxygen uptake was markedly decreased with all substrates in the E47 extracts. Vitamin E completely prevented the decrease in oxygen uptake. Under conditions of CYP2E1 overexpression, two modes of CYP2E1 dependent toxicity can be observed in Hep G2 cells: a slower growth rate when cellular GSH levels are maintained and a loss of cellular viability when cellular GSH levels are depleted. Elevated lipid peroxidation plays an important role in the CYP2E1 dependent toxicity and apoptosis. This direct toxicity of overexpressed CYP2E1 may reflect the ability of this enzyme to generate reactive oxygen species even in the absence of added metabolic substrate.

L29 ANSWER 5 OF 17 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1998:29945 BIOSIS
DOCUMENT NUMBER: PREV199800029945
TITLE: Caspase-mediated apoptosis in AK-5 tumor cells: A cell-free study using peptide inhibitors and antisense strategy.
AUTHOR(S): Anjum, Rana; Khar, Ashok (1)
CORPORATE SOURCE: (1) Cent. Cellular Molecular Biol., Hyderabad 500 007 India
SOURCE: Experimental Cell Research, (**Nov. 1, 1997**) Vol. 236, No. 2, pp. 371-377.
ISSN: 0014-4827.
DOCUMENT TYPE: Article
LANGUAGE: English
AB An in vitro system has been employed to study the apoptotic mechanisms in the AK-5 tumor which is a spontaneously regressing rat histiocytoma. Cytosolic extracts of tumor cells primed for apoptosis using dexamethasone and immune serum from tumor-regressing animals were able to induce apoptosis in intact nuclei and reproduce the classical morphological and biochemical features typical of apoptotic cells. The cleavage of lamin A and PARP to signature fragments by these extracts and the inhibition of the same using peptide inhibitors signify the pivotal role of ICE and ICE-related proteases in apoptosis. Lamin A cleavage was insensitive to YVAD but PARP cleavage was blocked by both YVAD and DEVD. Cell extracts derived from cells overexpressing the **Bcl-2** gene and Nedd-2 **antisense** gene, respectively, failed to induce apoptosis in exogenously added nuclei, suggesting that **Bcl-2** gene product is downregulating a key event in apoptotic cascade. The study also demonstrates the coherent action of different ICE-related proteases in apoptosis and their functional redundancy. This system may prove useful for analyzing **complex** molecular mechanisms underlying apoptosis in tumor cells.

L29 ANSWER 6 OF 17 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1997:388488 BIOSIS

DOCUMENT NUMBER: PREV199799687691
TITLE: Mitochondrial implication in accidental and programmed cell death: Apoptosis and necrosis.
AUTHOR(S): Zamzami, Naoufal; Hirsch, Tamara; Dallaporta, Bruno; Petit, Patrice X.; Kroemer, Guido
CORPORATE SOURCE: Cent. Natl. de la Recherche Scientifique-UPR420, 19 rue Guy Moquet, B.P. 8, F-94801 Villejuif France
SOURCE: Journal of Bioenergetics and Biomembranes, (1997) Vol. 29, No. 2, pp. 185-193.
ISSN: 0145-479X.
DOCUMENT TYPE: General Review
LANGUAGE: English

AB Both physiological cell death (apoptosis) and at least some cases of accidental cell death (necrosis) involve a two-step-process. At a first level, numerous physiological or pathological stimuli can trigger mitochondrial permeability transition which constitutes a rate-limiting event and initiates the common phase of the death process. Mitochondrial permeability transition (PT) involves the formation of proteaceous, regulated pores, probably by apposition of inner and outer mitochondrial membrane proteins which cooperate to form the mitochondrial PT pore **complex**. Inhibition of PT by pharmacological intervention on mitochondrial structures or mitochondrial expression of the apoptosis-inhibitory oncoprotein **Bcl-2** thus can prevent cell death. At a second level, the consequences of mitochondrial dysfunction (collapse of the mitochondrial transmembrane potential, uncoupling of the respiratory chain, hyperproduction of superoxide anions, disruption of mitochondrial biogenesis, outflow of matrix calcium and glutathione, and release of soluble intermembrane proteins) can entail a bioenergetic catastrophe culminating in the disruption of plasma membrane integrity (necrosis) and/or the activation and action of apoptogenic proteases with secondary endonuclease activation and consequent **oligonucleosomal** DNA fragmentation (apoptosis). The acquisition of the biochemical and ultrastructural features of apoptosis critically relies on the liberation of apoptogenic proteases or protease activators from the mitochondrial intermembrane space. This scenario applies to very different models of cell death. The notion that mitochondrial events control cell death has major implications for the development of death-inhibitory drugs.

L29 ANSWER 7 OF 17 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1996:563686 BIOSIS
DOCUMENT NUMBER: PREV199799293042
TITLE: Effects of 1,25 dihydroxyvitamin D-3 and its analogues on induction of apoptosis in breast cancer cells.
AUTHOR(S): James, Sharon Y.; Mackay, Alan G.; Colston, Kay W. (1)
CORPORATE SOURCE: (1) Dep. Clinical Biochem., St. George's Hosp. Med. Sch., London, SW17 ORE UK
SOURCE: Journal of Steroid Biochemistry and Molecular Biology, (1996) Vol. 58, No. 4, pp. 395-401.
ISSN: 0960-0760.
DOCUMENT TYPE: Article
LANGUAGE: English

AB Vitamin D derivatives have been shown both to inhibit the proliferation of cultured breast cancer cells and to cause regression of experimental mammary tumours in vivo. We have investigated the ability of several vitamin D analogues to promote the regression of experimental rat mammary tumours. Our results revealed that one vitamin D compound in particular, EB1089 (1(S),3(R)-dihydroxy-20(R)-5'-ethyl-5'-hydroxy-hepta-1'(E),3'(E)-dien-1'-yl)-9,10-secopregna-5(Z),7(E),10(19)-triene), was highly effective at inhibiting tumour progression, without causing a significant rise in serum calcium concentration. Tumour regression occurs when the rate of cell death is greater than the rate of cell proliferation. Apoptosis (programmed or active cell death) is an active, energy-dependent process

in which a distinct series of biochemical and molecular events leads to the death of cells by specific signals. We have examined effects of 1,25-dihydroxyvitamin D-3 (1,25(OH)-2D-3) and the synthetic vitamin D analogue EB1089 on indices of apoptosis in cultured human breast cancer cells. The effects of the vitamin D compounds on the expression of two oncoproteins which may regulate apoptosis, **bcl-2** and p53 were examined by Western analysis. In MCF-7 cell cultures treated for six days with 1,25(OH)-2D-3 or EB1089 (1 times 10-8 M), **bcl-2** protein was reduced in comparison to control levels, whereas p53 protein was increased. In addition, the p21 protein, whose gene WAF-1 is induced by wild type p53, was also increased by both vitamin D compounds. Using Northern analysis, it was observed that 24-h treatment of MCF-7 cells with 1 times 10-8 M 1,25(OH)-2D-3 or EB1089 resulted in an induction of TRPM-2 (clusterin) mRNA, a gene associated with onset of apoptosis in the involuting prostate. Fragmentation of genomic DNA is a characteristic feature of apoptosis. With the terminal deoxynucleotidyl transferase (TdT) assay, 3'-OH DNA breaks indicative of DNA fragmentation were detected histochemically in MCF-7 cells treated with 1 times 10-8 M 1,25(OH)-2D-3 or EB1089 for four days prior to fixation and TdT reaction. Further evidence of apoptosis was obtained following six days treatment of MCF-7 cell cultures with 5 times 10-8 M 1,25(OH)-2D-3 or EB1089, utilizing a cell death ELISA assay, which measures the presence of histone-associated **oligonucleosome complexes** generated from DNA fragmentation. Taken together our findings indicate that vitamin D derivatives may play a role in regulating the expression of genes and protein products implicated in apoptosis.

L29 ANSWER 8 OF 17 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1996:284225 BIOSIS
DOCUMENT NUMBER: PREV199699006581
TITLE: Antigen-specific apoptosis in immortalized T cells by soluble MHC class II-peptide complexes.
AUTHOR(S): Arimilli, Subhashini; Mumm, John B.; Nag, Bishwajit (1)
CORPORATE SOURCE: (1) Anergen Inc., 301 Penobscot Dr., Redwood City, CA 94063 USA
SOURCE: Immunology and Cell Biology, (1996) Vol. 74, No. 1, pp. 96-104.
ISSN: 0818-9641.
DOCUMENT TYPE: Article
LANGUAGE: English

AB The recognition of T cell receptors (TCR) by purified major histocompatibility **complex** (MHC) class II-peptide **complexes** in the absence of costimulatory signals leads to the induction of T cell nonresponsiveness or anergy. In a recent study using human T cell clones, it was observed that prolonged incubation of resting T cells with soluble MHC 11-peptide **complexes** appears to result in T cell apoptosis. The present study shows that the engagement of TCR by soluble MHC II-peptide **complexes** also results in antigen-specific apoptosis in immortalized T cells. Apoptosis was demonstrated in a herpes saimiri virus (HSV) transformed human T cell clone (SS8T) restricted for HLA-DR2 in association with an epitope from the myelin basic protein (MBP(84-102)). A dose- and time-dependent T cell death was observed upon incubation of SS8T cloned T cells with purified **complexes** of native human HLA-DR2 and MBP(83-102)Y-83 peptide. The specificity of T cell apoptosis was demonstrated by exposing SS8T cells with DR2 alone and DR2 bound to another high affinity epitope (MBP(124-143)) from the same MBP. Recently, we have shown that the **complexes** of HLA-DR2 and (MBP(83-102)Y-83) can be reconstituted by refolding Escherichia coli expressed individual DR2 alpha and beta (B5*0101) polypeptide chains lacking the transmembrane region. When SS8T cloned T cells were exposed to purified reconstituted rDR2.MBP(83-102)Y-83 **complexes**, similar apoptosis of T cells was observed. Agarose gel analysis of T cells incubated with **complexes** showed a

degradation of cellular deoxyribonucleic acid (DNA) to **oligonucleosomal** bands, a characteristic of apoptosis. The quantitative detection of DNA strand breaks was performed by pulsing T cells with 5-bromo-2'-deoxyuridine (BrdU) followed by the detection of BrdU-labelled DNA fragments using an antibody sandwich enzyme-linked immuno assay (ELISA). The fragmentation of DNA was also measured by double fluorescence flow cytometry by 3' end labelling of fragmented DNA with biotinylated-deoxyuridine triphosphate (dUTP) in the presence of terminal deoxynucleotide transferase (TdT) enzyme. The expression of the **bcl-2** protein in SS8T cells following TCR engagement by soluble MHC II-peptide **complexes** was monitored by chemiluminescence blot analysis using anti-**bcl-2** monoclonal antibody. Finally, the nucleosomal condensation of T cells following **complex** treatment, characteristics of typical apoptosis, was demonstrated by transmission electron microscopy. These results suggest that the binding of soluble MHC class II-peptide **complexes** to TCR induces antigen-specific apoptosis in transformed CD4 positive T cells in vitro. Such induction of apoptosis by soluble MHC II-peptide **complexes** may provide a novel therapeutic strategy to delete autoreactive T cells in various autoimmune diseases.

L29 ANSWER 9 OF 17 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1996:283498 BIOSIS
DOCUMENT NUMBER: PREV199699005854
TITLE: Binding of DNA oligonucleotides to sequences in the promoter of the human bcl-2 gene.
AUTHOR(S): Olivas, Wendy M.; Maher, L. James, III (1)
CORPORATE SOURCE: (1) Dep. Biochem. Mol. Biol., Mayo Foundation, 200 First St., SW, Rochester, MN 55905 USA
SOURCE: Nucleic Acids Research, (1996) Vol. 24, No. 9, pp. 1758-1764.
ISSN: 0305-1048.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Duplex DNA recognition by **oligonucleotide**-directed triple helix formation is being explored as a highly specific approach to artificial gene repression. We have identified two potential triplex target sequences in the promoter of the human **bcl-2** gene, whose product inhibits apoptosis. **Oligonucleotides** designed to bind these target sequences were tested for their binding affinities and specificities under pseudophysiological conditions. Electrophoretic mobility shift and dimethyl sulfate footprinting assays demonstrated that an **oligonucleotide** designed for simultaneous recognition of homopurine domains on alternate duplex DNA strands had the highest affinity of any **oligonucleotide** tested. Modifications to render this **oligonucleotide** nuclease-resistant did not reduce its binding affinity or specificity. In additional studies under various pH conditions, pyrimidine motif **complexes** at these target sequences were found to be stable at pH 8.0, despite the presumed requirement for protonation of **oligonucleotide** cytidines. In contrast, purine motif **complexes**, typically considered to be pH independent, were highly destabilized at decreasing pH values. These results indicate that a natural sequence in the human **bcl-2** promoter can form a stable triplex with a synthetic **oligonucleotide** under pseudo-physiological conditions, and suggest that triple helix formation might provide an approach to the artificial repression of **bcl-2** transcription.

L29 ANSWER 10 OF 17 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1996:265227 BIOSIS
DOCUMENT NUMBER: PREV199698821356
TITLE: Induction of hepatoma cell apoptosis by c-myc requires zinc and occurs in the absence of DNA fragmentation.

AUTHOR(S): Xu, Jun; Xu, Yang; Nguyen, Quynh; Novikoff, Phyllis M.; Czaja, Mark J. (1)
CORPORATE SOURCE: (1) Marion Bessin Liver Res. Cent., Albert Einstein Coll. Med., 1300 Morris Park Ave., Bronx, NY 10461 USA
SOURCE: American Journal of Physiology, (1996) Vol. 270, No. 1 PART 1, pp. G60-G70.
ISSN: 0002-9513.
DOCUMENT TYPE: Article
LANGUAGE: English

AB Since c-myc expression is increased during apoptosis in toxin-induced liver injury in vivo, the role of c-myc in liver cell apoptosis was investigated. The human hepatoma cell line HuH-7, which constitutively expresses c-myc, was stably transfected with sense and **antisense** c-myc expression vectors under the control of the zinc-inducible metallothionein promoter. None of the three cell types (wild-type, sense c-myc, or **antisense** c-myc) underwent apoptosis when cultured in serum-free medium (SFM). With the addition of SFM plus 37.5 mu-M zinc, wild-type and sense c-myc-expressing cells underwent rapid cell death, whereas **antisense** c-myc-expressing cells exhibited increased survival. This cell death had the light, fluorescent, and electron microscopic appearance of apoptosis, but did not result in DNA fragmentation. This apoptosis could be terminated by the addition of medium containing 2% fetal calf serum or the overexpression of **bcl-2** but not by supplementation with specific growth factors. Altering c-myc expression did not affect cellular metallothionein mRNA levels or the rate of cell death from copper or cadmium. The requirement for zinc and absence of DNA fragmentation in c-myc-induced hepatoma cell apoptosis under serum-free conditions provides further evidence of the **complex** regulation of apoptosis in different cell types.

L29 ANSWER 11 OF 17 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1994:407670 BIOSIS
DOCUMENT NUMBER: PREV199497420670
TITLE: Bcl-2 proto-oncogene and Epstein-Barr virus latent membrane protein-1 expression in AIDS-related lymphoma.
AUTHOR(S): Schlaifer, D. (1); Brousset, P.; Attal, M.; Massip, P.; Payen, C.; Marchou, B.; Huguet, F.; Muller, C.; Laurent, G.; et al.
CORPORATE SOURCE: (1) Serv. d'Hematologie, Clinique Dieulafoy, Centre Hosp. Regional, Hopital Purpan, Place Docteur Baylac, 31059 Toulouse Cedex France
SOURCE: Histopathology (Oxford), (1994) Vol. 25, No. 1, pp. 77-82.
ISSN: 0309-0167.
DOCUMENT TYPE: Article
LANGUAGE: English

AB The expression of **bcl-2** protein and Epstein-Barr virus (EBV) latent membrane protein 1 (LMP-1) was investigated in 18 cases of lymphoma occurring in the acquired immunodeficiency syndrome (AIDS). EBV small RNAs were detectable in tumour cells in all cases by in situ hybridization with EBER **oligonucleotides**. LMP-1 expression was detected in 61% of the cases, and 55% were positive for **bcl-2**. Dual expression of LMP-1 and **bcl-2** was found in 8/18 (44%) cases, while five cases (28%) expressed either LMP-1 or **bcl-2** and five expressed neither. Thus, there was an inconsistent relationship between the presence of EBV and the expression of **bcl-2**. One LMP-1 negative case was found to express **bcl-2** in reactive lymphocytes but not in lymphoma cells. No clinical features were found to correlate statistically with LMP-1 or **bcl-2** expression in the tumour cells. However, CD4 counts at diagnosis were significantly lower in **bcl-2** positive cases (P lt 0.05). The respective roles of EBV LMP-1 and the expression of **bcl-2** in lymphogenesis in AIDS patients remains **complex** and is not yet fully understood.

L29 ANSWER 12 OF 17 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1994:129659 BIOSIS
DOCUMENT NUMBER: PREV199497142659
TITLE: H-2-z homozygous New Zealand mice as a model for B-cell chronic lymphocytic leukemia: Elevated bcl-2 expression in CD5 B cells at premalignant and malignant stages.
AUTHOR(S): Okamoto, Hiroshi; Nishimura, Hiroyuki; Shinozaki, Ayako; Zhang, Danqing; Hirose, Sachiko; Shirai, Toshikazu (1)
CORPORATE SOURCE: (1) Dep. Pathology, Juntendo Univ. Sch. Med., 2-1-1 Hongo, Bunkyo-ku, Tokyo 113 Japan
SOURCE: Japanese Journal of Cancer Research, (1993) Vol. 84, No. 12, pp. 1273-1278.
ISSN: 0910-5050.
DOCUMENT TYPE: Article
LANGUAGE: English
AB In New Zealand mice, the major histocompatibility **complex** (MHC) controls the development of both autoimmune disease and B cell chronic lymphocytic leukemia (B-CLL). While H-2-d/H-2-z heterozygosity acts as one major predisposing genetic element for autoimmune disease, H-2-z/H-2-z homozygosity acts as an element for B-CLL. In the H-2-z/H-2-z homozygotes, there was an age-dependent increase in frequencies of CD5 B cells in the blood and spleen, and such CD5 B cells showed **oligoclonal** to monoclonal expansion, giving rise to B-CLL. B-CLL cells from these mice had surface phenotypes typical of CD5 B lineage cells, and expressed high levels of proto-oncogene **bcl-2**. Elevated **bcl-2** expression was also observed in premalignant B cells in the aged mice, thereby suggesting that apoptosis-resistant, long-surviving CD5 B cells with a self-renewal capacity form the basis of malignant transformation. This model not only provides clues for analyzing multiple steps of genetic alterations involved in the generation of B-CLL, but also sheds light on the correlation between B-CLL and autoimmune disease.

L29 ANSWER 13 OF 17 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1998294990 EMBASE
TITLE: Modulation of stem cell proliferation by anticytokine or antisense oligonucleotide strategy in hematological malignancies.
AUTHOR: Milenkovic P.
CORPORATE SOURCE: Prof. P. Milenkovic, Institute for Medical Research, Dr Subotica 4, 11000 Belgrade, Yugoslavia
SOURCE: Archive of Oncology, (1998) 6/3 (115-117).
Refs: 32
ISSN: 0354-7310 CODEN: ARONFV
COUNTRY: Yugoslavia
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
022 Human Genetics
025 Hematology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Continuous proliferation and differentiation of hemopoietic cells are controlled by **complex** interactions and genetically determined production of stimulatory and inhibitory regulatory molecules. In hematological malignancies clonal expansion of transformed hemopoietic stem cells (HSC) is related to changes in oncogene expression (ras, myc, fos, mpl, kit...) leading to impaired production/response to regulatory molecules. In recent years a number of diverse therapy strategies have been evaluated in the development of novel therapeutic modalities. Selected approaches involve cytokine/anticytokine, **antisense oligonucleotide**, inhibition of intracellular signal transduction and gene therapy. Reduction of the level or activity of cytokines as cell

viability factors (inhibitors of cytokine synthesis, antibodies to cytokine receptors...) consequently enhances and induces apoptotic action of hemotherapeutic agent. The use of **antisense oligonucleotides** (c-myb or c-myc **antisense oligonucleotides**, inhibition of **bcl-2**, reversal of multidrug resistance by mdr1 **antisense oligonucleotide**...) are currently extensively studied in vitro and in vivo. New approaches in inhibition of intracellular signal transduction involve a down regulation of oncogene expression. More specific studies involve potentials of gene-target selective destruction of leukemic cells containing bcr-c-abl fusion gene.

L29 ANSWER 14 OF 17 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 97126683 EMBASE
DOCUMENT NUMBER: 1997126683
TITLE: Antisense oligonucleotides as therapeutics for malignant diseases.
AUTHOR: Ho P.T.C.; Parkinson D.R.
CORPORATE SOURCE: Dr. P.T.C. Ho, DCTDC, Investigational Drug Branch, National Cancer Institute, 6130 Executive Blvd., Rockville, MD 20852, United States
SOURCE: Seminars in Oncology, (1997) 24/2 (187-202).
Refs: 103
ISSN: 0093-7754 CODEN: SOLGAV
COUNTRY: United States
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 016 Cancer
022 Human Genetics
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The continued progress in our understanding of the biology of neoplasia and in the identification, cloning, and sequencing of genes critical to tumor cell function permits the exploitation of this information to develop specific agents that may directly modulate the function of these genes or their protein products. **Antisense oligonucleotides** are being investigated as a potential therapeutic modality that takes direct advantage of molecular sequencing. The **antisense** approach uses short **oligonucleotides** designed to hybridize to a target mRNA transcript through Watson-Crick base pairing. The formation of this **oligonucleotide**: RNA heteroduplex results in mRNA inactivation and consequent inhibition of synthesis of the protein product. A fundamental attraction of the **antisense** approach is that this method potentially may be applied to any gene product, in theory, for the treatment of malignant and non-malignant diseases. However, this simple and attractive model has proven to be much more **complex** in practice. A number of important challenges in the preclinical development of **antisense oligonucleotides** have been identified, including stability, sequence length, cellular uptake, target sequence selection, appropriate negative controls, **oligonucleotide**: protein interactions, and cost of manufacture. Although the biological activity of an **oligonucleotide** against its molecular target is theoretically sequence-dependent, the animal pharmacokinetics and toxicology of phosphorothioate analogues directed against vastly disparate gene products appear relatively non-sequence-specific. In oncology, a number of clinical trials have been initiated with **antisense oligonucleotides** directed against molecular targets including: p53; **bcl-2**; rof kinase; protein kinase C-.alpha.; c-myb. The experience gained from these early clinical trials will be applicable to the next generation of **antisense** agents in development. These may include molecules with novel backbones or other structural modifications, chimeric **oligonucleotides**, or peptide nucleic acids. Continued progress in this arena will require that many of

the preclinical challenges confronting **antisense** development are satisfactory resolved.

L29 ANSWER 15 OF 17 CA COPYRIGHT 2003 ACS
ACCESSION NUMBER: 129:130966 CA
TITLE: A study of synthetic porphyrin oligodeoxynucleotide conjugates on lymphoma and leukemia cells in vitro
AUTHOR(S): Ma, D. D. F.; Rede, T.; Dickson, L.; Naqvi, N.
CORPORATE SOURCE: Department of Haematology, Royal North Shore Hospital, St Leonards, 2065, Australia
SOURCE: Nucleic Acids Symposium Series (**1998**), 38(Advances in Gene Technology: Molecular Biology in the Conquest of Disease), 175-176
CODEN: NACSD8; ISSN: 0261-3166
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The biol. activity of oligodeoxynucleotides (ODNs) conjugated to porphyrin derivs. on human cancer cells was investigated. Porphyrin-ODN conjugates enhance cellular uptake, retard enzymic degrdn. and provide site directed chem. reaction with the targeted nucleic acid. Porphyrin-ODN conjugates targeted against the initiation sites of bcl-2 and c-myb mRNA were tested. The cell culture results show that **bcl-2** and c-myb **antisense** porphyrin **conjugates** were more efficient in inhibiting tumor growth than unconjugated ODNs and **conjugated** controls. The improved efficacy of these conjugates might be due to increased nuclease resistance and improved cellular uptake imparted by the incorporation of the porphyrin derivs.
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L29 ANSWER 16 OF 17 CA COPYRIGHT 2003 ACS
ACCESSION NUMBER: 127:302975 CA
TITLE: The synergistic cytotoxic effect of a doxorubicin immunoconjugate and bcl-2 antisense oligonucleotides on non-resistant and drug resistant small cell lung cancer cell lines
AUTHOR(S): Froesch, B. A.; Luedke, G. H.; Ziegler, A.; Stahel, R. A.; Zangemeister-Wittke, U.
CORPORATE SOURCE: Department of Internal Medicine, Division of Oncology, University Hospital, Zurich, CH-8044, Switz.
SOURCE: Tumor Targeting (**1996**), 2(5/6), 265-276
CODEN: TUTAF9; ISSN: 1351-8488
PUBLISHER: Chapman & Hall
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Resistance to chemotherapy is a major cause for failure in the treatment of small cell lung cancer (SCLC) and is assocd. with genetic alternations affecting drug activity and the regulation of apoptosis. As an approach to more effective second-line treatment of SCLC, a combination of antisense-mediated downregulation of bcl-2 expression and targeted delivery of doxorubicin (DOX) using the epithelial glycoprotein-2 (EGP-2)-specific immunoconjugate MOC31-DOX was examd. As demonstrated on different SCLC cell lines, the cytotoxic effects of DOX and MOC31-DOX were comparable, but the immunoconjugate was more than 100-fold more specific for EGP-2-pos. tumor cells. Despite internalization via endocytosis, MOC31-DOX could not overcome chemoresistance mediated by P-glycoprotein. Treatment of cells with antisense oligodeoxynucleotides (AS-ODNs) complementary to the bcl-2 mRNA significantly reduced bcl-2 expression in a sequence-specific manner. In correlation with the basal bcl-2 expression levels of the cell lines, this treatment induced apoptosis in up to 90% of tumor cells. In cell proliferation and colony-forming assays, the combination of bcl-2 antisense and MOC31-DOX resulted in a

potent synergistic cytotoxic effect on all cell lines. This finding suggests the therapeutic use of bcl-2 AS-ODNs as an adjunct to tumor-targeted chemotherapy for the treatment of chemoresistant SCLC.

L29 ANSWER 17 OF 17 SCISEARCH COPYRIGHT 2003 ISI (R)
ACCESSION NUMBER: 96:119845 SCISEARCH
THE GENUINE ARTICLE: TT394
TITLE: INDUCTION OF HEPATOMA-CELL APOPTOSIS BY C-MYC REQUIRES ZINC AND OCCURS IN THE ABSENCE OF DNA FRAGMENTATION
AUTHOR: XU J (Reprint); XU Y; NGUYEN Q; NOVIKOFF P M; CZAJA M J
CORPORATE SOURCE: YESHIVA UNIV ALBERT EINSTEIN COLL MED, MARION BESSIN LIVER RES CTR, 1300 MORRIS PK AVE, BRONX, NY, 10461 (Reprint); YESHIVA UNIV ALBERT EINSTEIN COLL MED, DEPT MED, BRONX, NY, 10461; YESHIVA UNIV ALBERT EINSTEIN COLL MED, DEPT PATHOL, BRONX, NY, 10461
COUNTRY OF AUTHOR: USA
SOURCE: AMERICAN JOURNAL OF PHYSIOLOGY-GASTROINTESTINAL AND LIVER PHYSIOLOGY, (**JAN 1996**) Vol. 33, No. 1, pp. G60-G70.
ISSN: 0193-1857.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: ENGLISH
REFERENCE COUNT: 48

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Since c-myc expression is increased during apoptosis in toxin-induced liver injury in vivo, the role of c-myc in liver cell apoptosis was investigated. The human hepatoma cell line HuH-7, which constitutively expresses c-myc, was stably transfected with sense and **antisense** c-myc expression vectors under the control of the zinc-inducible metallothionein promoter. None of the three cell types (wild-type, sense c-myc, or **antisense** c-myc) underwent apoptosis when cultured in serum-free medium (SFM). With the addition of SFM plus 37.5 mu M zinc, wild-type and sense c-myc-expressing cells underwent rapid cell death, whereas **antisense** c-myc-expressing cells exhibited increased survival. This cell death had the light, fluorescent, and electron microscopic appearance of apoptosis, but did not result in DNA fragmentation. This apoptosis could be terminated by the addition of medium containing 2% fetal calf serum or the overexpression of **bcl -2** but not by supplementation with specific growth factors. Altering c-myc expression did not affect cellular metallothionein mRNA levels or the rate of cell death from copper or cadmium. The requirement for zinc and absence of DNA fragmentation in c-myc-induced hepatoma cell apoptosis under serum-free conditions provides further evidence of the **complex** regulation of apoptosis in different cell types.

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